

Scientific Basis for Clinical Practice in Gastroenterology and Hepatology

A.B.R. Thomson

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THE WESTERN WAY

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Prologue

Like any good story, there is no real beginning or ending, just an in-between glimpse of the passing of time, a peek into a reality of people's minds, thoughts, feelings, and beliefs. The truth as I know it has a personal perspective which drifts into the soul of creation. When does life begin, when does an idea become conceived, when do we see love or touch reality? A caring, supportive, safe, and stimulating environment creates the holding blanket, waiting for the energy and passion of those who dream, invent, create – disrupt the accepted, challenge the conventional, ask the questions with forbidden answers. Be a child of the 60's. Just as each of us is a speck of dust in the greater humanity, the metamorphosis of the idea is but a single sparkle in the limitlessness of the Divine Intelligence. We are the ideas, and they are us. No one of us is truly the only parent of the idea, for in each of us is bestowed the intertwined circle of the external beginning and the end....

The child will grow, the images will expand, the learning of all aspects of our craft will develop and flourish amongst persons of good will. Examinations will become second nature, as each clinical encounter, each person, each patient, becomes our test, the determination of clinical competence, of caring, of compassion. May these three C's become part of each of our lives narrative. And from this start comes Capstone Academic Publishing, an innovation for the highest quality and value in educational material, made available at cost, speaking in tongues, in the languages of many cultures, with the dialect of the true North strong and free, so that knowledge will be available to all.

Outstanding medical practice and true dedication to those from whom we receive both a privilege and pleasure of care, comes within, comes from those rare teachers who inspire us. True, we need all of these to jump over a very high bar. But to be a truly outstanding physician, you need to care for and care about people, and you must respect the dignity and rights of all others. You must strike a balance between love and justice, and you place your family and friends at the top of your wish-list of lifetime achievements.

For the skeptics who ask "What do you want from me?" I simply say "You are the future; I trust that in time you too will help young people to be the best they can be."

May good luck, good health, modesty, peace, and understanding be with you always. Through medicine, all persons of the world may come to share caring, respect, dignity, and justice.

Sincerely,



Emeritus Distinguished University Professor, University of Alberta
Adjunct Professor, Western University

“They may forget what you said, but they will never forget how you made them feel.”

Carl W. Buechner, on teaching.

“With competence, care for the patient. With compassion, care about the person.”

Alan B. R. Thomson, on being a physician.

Dedication

To

Rebecca, Maxwell, Megan Grace, Henry and Felix

You fill the world with joy.

You promise the hope of a future of Love, Justice and Peace.

“With glowing hearts

we see thee rise.”

Acknowledgments

Patience and patients go hand in hand. So also does the interlocking of young and old, love and justice, equality and fairness. No author can have thoughts transformed into words, no teacher can make ideas become behavior and wisdom and art, without those special people who turn our minds to the practical - of getting the job done!

Thank you, Naiyana and Duen, for translating those terrible scribbles, called my handwriting, into the still magical legibility of the electronic age. Thank you, Sarah, for your creativity and hard work. Becky, thank you for your marvelous artistry. My most sincere and heartfelt thanks go to the excellent persons at JP Consulting, and CapStone Academic Publishers. Jessica, you are brilliant, dedicated and caring. Thank you.

When Rebecca, Maxwell, Megan Grace, Henry and Felix ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding and kind. For what I was trying to say and to do was to make my professional life focused on the three C's - competence, caring, and compassion - and to make my very private personal life dedicated to family - to you all.

Clinical physiological challenges

Control of Food Intake

CLINICAL PHYSIOLOGICAL CHALLENGE

Case: There is a world-wide epidemic in the development of increased BMI (aka obesity), and with this the onset of numerous weight-associated diseases. Your patient is an educated, sophisticated 45 year old CEO. She has undertaken a literature search to learn more about the pro's and con's of dieting versus exercise. She has already consulted an exercise physiologist, and now consults you to learn about how she can modify her food intake in order to loose weight.

Question: What are the mechanisms involved in the control of food intake?

→ In your answer, give the role of each of the following:

1. Mouth and GI tract
2. Adipocyte, Leptin, Insulin, Ghrelin, Incretins
3. POMC – secreting neurons (pro – opoimelanocortin)
4. ARC (arcuate nucleus)
5. PVN (paraventricular nucleus), LHN (lateral hypothalamic area hunger centre)
6. NTS (nuclear tractus solitaires)
7. CCK and GLP-1
8. PYY
9. Orexigenic pathyways
10. Anorexigenic pathways

CLINICAL PHYSIOLOGICAL CHALLENGE – meal size of a person with obesity

Case: Thinking back to the previous case, what are the factors which increase or decrease the size of meals?

- Factors which increase meal size (orexigenic effect)
 - Ghrelin stimulates NTS in brainstem.
 - CCK and secretin are released from ECL cells by intraluminal releasing factors (e.g., CCK releasing factor [CCK-RF]).
 - With food intake, CCK-RF stimulates CCK release into the blood. As the food stimulus lessens, trypsin in the intestinal lumen digests CCK-RF, and the release of CCK is diminished.
- Factors which reduce meal size (anorexigenic effect)
 - Cholecystokinin (CCK)
 - Glucagon-like peptide-2 (GLP-1)
 - Peptide tyrosine (PYY₃₋₃₆)
 - Gastrin releasing peptide (GRP)
 - Amylin
 - Apolipoprotein A-IV
 - Somatostatin
 - Leptin

Mouth and Salivary Glands

CLINICAL PHYSIOLOGICAL CHALLENGE – salivary secretion

Background: Salivary acinar cells secrete KHCO_3 and absorb NaCl . The apical (luminal) membrane contains a Na^+/H^+ , $\text{Cl}^-/\text{HCO}_3^-$ and a H^+/K^+ exchanger as well as epithelial Na^+ channels (ENaC) and CFTR (cystic fibrosis transmembrane regulator). The basolateral membrane contains a Na^+/H^+ exchanger, NaHCO_3 cotransporter, Na^+/K^+ ATPase, as well as K^+ channels and non-CFTR Cl^- channels.

Problem: With these components, draw a diagram which depicts the steps in the salivary secretion of fluid and electrolytes.

CLINICAL PHYSIOLOGICAL CHALLENGE – Salivary secretion

Background: The salivary gland is innervated by the parasympathetic and sympathetic nervous systems.

Problem: Provide the explanation for the development of xerostomia in some persons with Sjogren's syndrome, or treated with anticholinergics.

CLINICAL PHYSIOLOGICAL CHALLENGE – Xerostomia

Background: The salivary gland is innervated by the parasympathetic and sympathetic nervous systems.

Problem: Provide the explanation for the development of xerostomia in some persons with Sjogren's syndrome, or treated with anticholinergics.

Esophagus

CLINICAL PHYSIOLOGICAL CHALLENGE – GERD: "Reflux" disease

Case: A 45 year old man with an increased BMI of 29 began to develop severe retrosternal burning discomfort and acid regurgitation when his new –onset hypertension was treated with a calcium channel blocker. His symptoms of gastroesophageal reflux disease (GERD) were worsened by bending forward after meals, and by eating chocolate.

Questions: What is the physiology of GERD?

→ In giving your answer, please include the manometric pressure values of the upper (UES) and lower esophageal sphincter (LES), as well as the characteristics of the peristaltic waves of the esophageal body

- Structure and function of esophagus
- Tone and relaxation of LES
- Peripheral and central pathways mediating transient lower esophageal sphincter relaxations
- Conditions associated with GERD
- Maintenance of integrity of esophageal mucosal membrane

CLINICAL PHYSIOLOGICAL CHALLENGE - Dysphagia

Case: A 45 year old woman develops painless difficulty with swallowing liquids. She has no ENT symptoms, and a barium swallow and EGD (esophagogastroduodenoscopy) are normal. She is suspected as having an esophageal motility disorder.

Questions: Give the physiology of swallowing and describe the features of an esophageal motility tracing which characterize three motility disorders of the esophagus.

CLINICAL PHYSIOLOGICAL CHALLENGE – Pathophysiology of GERD

Case: A 45 year old man with an increased BMI of 29 began to develop severe retrosternal burning discomfort and acid regurgitation when his new –onset hypertension was treated with a calcium channel blocker. His symptoms of gastroesophageal reflux disease (GERD) were worsened by bending forward after meals, and by eating chocolate.

Questions: What is the pathophysiology of GERD?

→ In giving your answer, please include the manometric pressure values of the upper (UES) and lower esophageal sphincter (LES), as well as the characteristics of the peristaltic waves of the esophageal body

- Structure and function of esophagus
- Tone and relaxation of LES
- Peripheral and central pathways mediating transient lower esophageal sphincter relaxations
- Conditions associated with GERD
- Maintenance of integrity of esophageal mucosal membrane

Stomach

CLINICAL PHYSIOLOGICAL CHALLENGE – Hypergastrinemia and Acid Hypersecretion

Case: A 35 year old man with dyspepsia and diarrhea was found on upper GI endoscopy to have three ulcers in the second portion of the duodenum. He did not take ASA or NSAIDs, and his antral biopsies taken before acid lowering therapy were negative for *H. pylori*. A fasting serum gastrin concentration was 750 pg/ml. You suspect that he may have a gastric hypersecretion state.

Question:

- Give the physiology of gastric secretion of hydrochloric acid and pepsinogen, the mechanisms of the control of acid secretion, and the pathophysiology of the hypergastrinemia and hyperacidemia seen in persons with gastrinoma
- Explain the scientific basis for the calcium – infusion and the secretin tests for Zollinger-Ellison Syndrome, and the rate of measuring BAO and MAO.
- Outline the mechanisms of diarrhea in this patient

Abbreviations: BAO, basal acid output; MAO, maximal acid output

CLINICAL PHYSIOLOGICAL CHALLENGE – Physiology of Gastric Acid Secretion

Background: Gastric parietal cells secrete hydrochloric acid (HCl). The apical (luminal) membrane contains H^+/K^+ ATPase, as well as a Cl^- and a K^+ channel. The basolateral membrane contains Na^+/K^+ ATPase, a Na^+/H^+ exchanger (NHE), as well as a K^+ and a HCO_3^-/Cl^- channel.

Problem: With these membrane components, draw a diagram which depicts the steps in the gastric parietal cell secretion of HCl and fluid.

CLINICAL PHYSIOLOGICAL CHALLENGE – Turning Acid Secretion On and Off

Background: The stomach has a series of integrated control systems to mediate the secretion of HCl and pepsin to initiate the process of digestion of food. But an excess of HCl and pepsin can damage the mucosa of the stomach and duodenum, causing ulceration with its associated problems of hemorrhage, obstruction and perforation.

Problem: Describe in detail how the stomach turns on and then turns off hydrochloric (HCl) acid secretion

CLINICAL PHYSIOLOGICAL CHALLENGE – Parietal cell

Background: Gastric parietal cells secrete hydrochloric acid (HCl). The apical (luminal) membrane contains H^+/K^+ ATPase, as well as a Cl^- and a K^+ channel. The basolateral membrane contains Na^+/K^+ ATPase, a Na^+/H^+ exchanger (NHE), as well as a K^+ and a HCO_3^-/Cl^- channel.

Problem: With these membrane components, draw a diagram which depicts the steps in the gastric parietal cell secretion of HCl and fluid.

CLINICAL CHALLENGE – Secretin Test for Gastrinoma

Case: A patient with aggressive peptic ulcer disease complicated by hypercalcemia and diarrhea has fasting hypergastrinemia. A secretin infusion test is undertaken to determine if the patient has biochemical evidence of gastrinoma.

Question: Give the explanation for the increase in the plasma concentration of gastrin following the injection of secretin in the patient with a gastrinoma.

CLINICAL PHYSIOLOGICAL CHALLENGE – MAO/BAO

Background:

- The ratio of gastric MAO/BAO (maximal acid output, divided by basal acid output) is much higher than the ratio of maximal to basal pepsinogen secretion.

Question:

- Why? Firstly, the Ach-responsive HCl secretion stimulates a local cholinergic reflex to release even more Ach, and thereby more pepsinogen from the chief cells. Secondly, when HCL empties into the duodenum, secretin is released from duodenal S cells, and secretin also stimulates the chief cells to secrete pepsinogen.

CLINICAL PHYSIOLOGICAL CHALLENGE – PK/ PD of PPIs

Case: When an 18 year old man's dyspepsia fails to respond to once a day proton pump inhibitor (PPI), he is reminded to take the medication half an hour before breakfast, and he now enjoys symptom relief.

Question: Give the pharmacokinetics and pharmacodynamics of PPIs and explain why PPIs must be taken half an hour before the intake of food

CLINICAL PHYSIOLOGICAL CHALLENGE – Peptic Ulcer Therapy

Case: Gastric fluid pH may be reduced by antacids, or by blockage of the histamine-2 (H₂) receptor or the H⁺/K⁺ - ATPase (the proton pump). Peptic ulcer disease develops for several reasons, including the damaging effects of H⁺ and pepsin on the gastric mucosa.

Questions: Apart from the proton pump inhibitors (PPI) producing a lower reduction of gastric acid secretion, what other mechanism likely contributes to their greater healing potential.

CLINICAL PHYSIOLOGICAL CHALLENGE - Gastroparesis

Case: A 28 year old diabetic man with poor insulin control of his hyperglycemia presents with post-prandial nausea, fullness and discomfort. He is diagnosed as having diabetic gastroparesis.

Question:

- a) Give 6 tests of gastric neurological function which might be used in this patient to document the suspected presence of gastroparesis.
- b) What are the pathophysiological defects which occur in diabetic gastroparesis, the resulting symptoms, and the potential pharmaceutical approaches to help correct the defects and relieve the symptoms?

CLINICAL PHYSIOLOGICAL CHALLENGE

Question: Draw the anatomy for three of the bariatric surgical procedures used for weight loss

Answer: See Figure above

CLINICAL PHYSIOLOGICAL CHALLENGE – Gastroparesis

Case: A 29 year-old diabetic lady develops bloating and fullness after meal. She diagnosed with possible gastroparesis, and is referred to you for management. You recommend alterations in her diet, and explain her choices of prokinetic agents.

Questions:

- What is the pathophysiology of gastroparesis (not just in this patient)?
- What is the basis for the dietary recommendations which you make?
- What are the receptors on smooth muscle which may be targeted for her pharmaceutical treatment?

CLINICAL PHYSIOLOGICAL CHALLENGE - Malabsorption

Case: A 65 year old man had a Billioth II gastric resection 25 years ago for failed ulcer healing when treated with an H_2 – receptor antagonist. He presents to you now with anemia and diarrhea. The stools are malodorous, and float.

Questions:

- What are the mechanisms for the digestion of iron- and vitamin B12 – containing foods?
- How are these normal processes deranged after gastric surgery?
- Give the pathophysiology of the diarrhea and steatorrhea which may arises as a result of gastric surgery.

Pancreas

CLINICAL PHYSIOLOGICAL CORRELATION

Background: Severe pancreatitis may be life-threatening, and may be caused by many factors including alcohol, drugs and gallstones.

Problem: What are the mechanisms by which the pancreas is protected from self-destruction (autodigestion)?

CLINICAL PHYSIOLOGICAL CHALLENGE – Pancreatic Dysfunction

Background: When the pancreas becomes chronically inflamed, such as with chronic pancreatitis from alcohol abuse, there is a decrease in enzyme secretion and activity, leading to reduced nutrient digestion, and thereby malnutrition.

Questions: Draw figures to explain the normal processes of pancreatic secretion of enzymes, HCO_3^- and fluid, the control of their secretion, and thereby faulty digestion.

CLINICAL PHYSIOLOGICAL CORRELATION – Pancreatic Fluid

Background: The pancreatic acinar cells secrete some NaCl and water. The apical (luminal) membrane contains Cl^- channels. The basolateral membrane contains Na^+/K^+ ATPase, $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporter and K^+ channels.

Problem: With these membrane components, draw a diagram which depicts the steps in the pancreatic acinar cell secretion of NaCl and fluid.

CLINICAL PHYSIOLOGICAL CORRELATION

Background: The pancreatic duct cells secrete NaHCO_3 and water. The apical (luminal) membrane contains a $\text{HCO}_3^-/\text{Cl}^-$ exchanger, CFTR (cystic fibrosis transmembrane regulator), and ORCO (outward rectifying Cl^- channel). The basolateral membrane contains Na^+/K^+ ATPase, $\text{Na}^+/\text{HCO}_3^-$ cotransporter, Na^+/H^+ exchanger (NHE), and K^+ channels.

Problem: With these membrane components, draw a diagram which depicts the steps in the pancreatic ductular cell secretion of NaHCO_3 and water.

CLINICAL PHYSIOLOGICAL CHALLENGE – Tests of Pancreatic Function

Case: A 45 year old alcoholic man complains of weight loss despite continued intake of food. Pancreatic insufficiency is suspected.

Question: Give the principles behind the secretin test of pancreatic function (administration of exogenous secretion and measurement of duodenal concentration of HCO_3^-), and the Lundt test meal ingestion of a standard mixed meal, and measurement of digestive enzyme activity in duodenal fluid.

CLINICAL PHYSIOLOGICAL CHALLENGE – Test the Pancreas

Case: A 45 year-old alcoholic with recurrent episodes of acute pancreatitis develops weight loss and diarrhea. Pancreatic insufficiency is suspected, and the attending physician wishes to test the pancreatic function in this man.

Question:

- Outline the process of normal pancreatic fluid secretion, and thereby explain the principle of the secretin test for pancreatic HCO_3^- secretion
- Describe the process of normal pancreatic secretion of enzymes and proenzymes, and thereby explain the principle of the Lundh test meal for pancreatic enzyme secretion
- Give the mechanisms by which the pancreas prevents autodigestion, including the normal post-prandial process of inhibition of the cephalic, gastric and intestinal phases of pancreatic secretion.

Hepatobiliary system

CLINICAL PHYSIOLOGICAL CHALLENGE: The Role of Liver in the Enterohepatic Circulation of Bile Acids

Case: A 50 year old women with proven primary biliary cirrhosis (PBC) develops pruritis.

Question: Describe the process of the hepatocyte sinusoidal uptake, synthesis, and canalicular secretion of the bile acids (steps in the enterohepatic circulation of bile acids).

CLINICAL PHYSIOLOGICAL CORRELATION – Cholangiocyte Function

Background: The cholangiocyte sinusoidal membrane (SM) contains the AE2 (anion exchanger, aka $\text{HCO}_3^-/\text{Cl}^-$ exchanger, as well as CFTR and non-CFTR Cl^- channels. The cholangiocyte basolateral membrane (BM) contains the Na^+/K^+ ATPase, Na^+/H^+ exchanger (NHE), and the NaHCO_3 transporter.

Problem: With these membrane components, draw a diagram which depicts the steps in the cholangiocyte secretion of NaHCO_3 and water.

CLINICAL PHYSIOLOGICAL CORRELATION – Gallbladder Absorption

Background: The basolateral membrane (BM) of the gallbladder epithelium $\text{Na}^+/\text{K}^+\text{ATPase}$, as well as K^+ , Cl^- and H_2O channels. The apical membrane (AM) contains both Na^+/H^+ exchanger (NHE) and $\text{HCO}_3^-/\text{Cl}^-$ exchanger, as well as H_2O channels.

Problem: With these membrane components, draw a diagram which depicts the absorption of H_2O by the gallbladder epithelium.

CLINICAL PHYSIOLOGICAL CORRELATION – Cholesterol Gallstones

Case: Interruption of the enterohepatic secretion, increased hepatic secretion of cholesterol, or decreased synthesis of bile acids, or impaired gallbladder motility may result in the formation of cholesterol gallstones. These may cause blockage of the cystic duct and cholecystitis blockage of the common bile duct and jaundice as well as cholangitis, and blockage of the pancreatic duct causing acute pancreatitis.

Question: Describe the pathophysiology of the formation of cholesterol gallstones

CLINICAL PHYSIOLOGICAL CHALLENGE – Control of Cholesterol Metabolism

Case: A 45 year old woman with primary biliary cirrhosis (PBC) has hypercholesterolemia and xanthelasma.

Questions: Outline the role of the liver in maintaining normal concentrations of cholesterol in the blood.

CLINICAL PHYSIOLOGICAL CORRELATION – Bilirubin Metabolism

Case: A 32 year old women develops malaise, abdominal discomfort and jaundice.

Question: Draw a picture of bilirubin metabolism to distinguish between prehepatic, hepatic and posthepatic causes of jaundice.

CLINICAL PHYSIOLOGICAL CHALLENGE

Case: A 45 year old woman with primary biliary cirrhosis (PBC) has hypercholesterolemia and xanthelasma.

Questions: Outline the role of the liver in maintaining normal concentrations of cholesterol in the blood.

CLINICAL PHYSIOLOGICAL CHALLENGE - Gallstones

Case: A 28 year old mother of four healthy children develops RUQ pain and tenderness. Acute cholecystitis is diagnosed.

Question:

- Describe the steps in the metabolism of bilirubin
- Outline the pathophysiology of the development of gallstones.
- Explain the colour of the urine and stools in persons with obstruction of the common bile duct (CBD)

CLINICAL PHYSIOLOGICAL CHALLENGE – Drug-induced Liver Injury

Case: An 18 year-old distraught first year medical student consumes 10 grams of acetaminophen plus 250 ml of vodka over a two hour interval. S(he) is brought to the ER when mental confusion was noted.

Question:

- What are the possible drug, environment and host factors involved in the pathogenesis of DILI (drug-induced liver injury)?
- Give the role of the metabolic and host immune systems in the pathogenesis of acetaminophen hepatotoxicity

CLINICAL PHYSIOLOGICAL CHALLENGE – Drug-induced Liver Injury

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Question:

- What are the possible drug, environment and host factors involved in the pathogenesis of DILI (drug-induced liver injury)?
- Give the role of the metabolic and host immune systems in the pathogenesis of acetaminophen hepatotoxicity

CLINICAL PHYSIOLOGICAL CHALLENGE – Fatty liver

Case: A 58 year old “Cuddly” grandmother suffering from type II diabetes (insulin resistance) is noted to have an elevated serum AST and ALT. Abdominal ultrasound confirms the clinical suspicion of fatty liver

Questions:

- Give the pathophysiological steps leading to non-alcoholic fatty liver disease (NAFLD)
- Outline the initiation and perpetuation steps leading to steatohepatitis and fibrosis
- “Go for Purple”: List the regulated changes in gene expression during activation of HSC (hepatic stellate cells)

CLINICAL PHYSIOLOGICAL CHALLENGE – Polycystic Liver Disease

Question: Give 5 steps involved in the pathogenesis of PLD.

Answer:

- Malformation of the ductal plate through an altered development program of the biliary ducts.
- Changes in Ca^{2+} and cAMP, lead to abnormal function of cilia.
- Changes in fluid secretion by the epithelia through CFTR (cystic fibrosis transmembrane conductance regulator)
- Increased proliferation of cholangiocytes through IL-6, EGF (epidermal growth factor), VEGF (vascular endothelial growth factor) angiopoietin-1, and IGF-1 (insulin-like growth factor-1).
- Autocrine and paracrine angiogenic signaling, by factors which stabilize or phosphorylate HIF (hypoxia-inducible factors)-1 α by way of mTOR or Raf / mitogen-activated protein kinase (MEK) / ERK.
- Remodeling of extracellular matrix (ECM)
- MMP (matrix metalloproteinase)-2 increases activity of portal myofibroblasts to allow for expansion of cysts.

CLINICAL PHYSIOLOGICAL CHALLENGE – Portal Hypertension

Case: A 45 year old man develops esophageal varices. He consumes over 20 ounces of alcohol a day, and is suspected to having portal hypertension (PHT) from cirrhosis.

Problem: Describe the portal circulation, define PHT, and explain the mechanism of development of PHT in prehepatic, intrahepatic and posthepatic disorders.

Small Intestine

CLINICAL PHYSIOLOGICAL CHALLENGE - Diarrhea

Case: A 25 year old woman returns from a holiday in a Central American Country, complaining of watery (non-fatty and non-bloody) diarrhea. She is unable to tolerate drinking milk because of bloating, excess flatus and worsening diarrhea; but taking a mixture of sugar and salt improves her dehydration.

Question

- What is the normal process of absorption of salt and water?
- Explain how the intestine normally protects itself from luminal bacteria.
- What is the scientific basis for the tests used to diagnose SIBO (small intestinal bacterial overgrowth)?
- Explain her lactose intolerance
- Give the scientific basis for the use of oral rehydration solutions

CLINICAL PHYSIOLOGICAL CHALLENGE – Celiac Disease

Case: Celiac disease (CD) is a condition which affects the luminal GI tract from the esophagus to the colon, as well as the liver, gallbladder, and pancreas. Think of any untreated celiac patient you have seen with malnutrition and multiple nutrient deficiencies.

Question: What is the pathophysiology of the maldigestion and malabsorption of carbohydrate, peptides and amino acids, lipids, folic acid and calcium in CD?

CLINICAL PHYSIOLOGICAL CORRELATION – More Diarrhea

Background: Diarrhea may result from an imbalance between intestinal secretagogues and absorptagogues. The treatment of diarrhea may include measures to normalize this imbalance.

Problem: Outline the role of the intestinal immune cells, endocrine cells and enteric nervous system in the control of fluid and electrolyte balance by the intestinal tract.

CLINICAL PHYSIOLOGICAL CORRELATION – Chloride Flux

Background: One process by which diarrhea occurs is through the decreased absorption of chloride (Cl^-) in the upper portion of the villus, and the increased secretion of Cl^- in the lower portion of the crypt-villus unit. The movement of Cl^- may be electroneutral or electrogenic and involves transporters and channels in the brush border membrane (AM) and the basolateral membrane (BM). Secretions of Cl^- is fundamental to the process of secretory diarrhea, such as occurs in cholera.

Problem: Draw a picture of Cl^- absorption and secretion from along the length of the small intestinal villus and in the colon.

CLINICAL PHYSIOLOGICAL CHALLENGE

Case: Celiac disease (CD) is a condition which affects the luminal GI tract from the esophagus to the colon, as well as the liver, gallbladder, and pancreas. Think of any untreated celiac patient you have seen with malnutrition and multiple nutrient deficiencies.

Question: What is the pathophysiology of the maldigestion and malabsorption of carbohydrate, peptides and amino acids, lipids, folic acid and calcium in CD?

CLINICAL PHYSIOLOGICAL CHALLENGE – Water Absorption

Background: Water may be absorbed through the brush border membrane, or between the enterocytes. A person takes sips of water throughout the day, and with a meal.

Problem: Draw a picture of the absorption of water from along the intestinal tract where the person is eating, or just drinking water.

CLINICAL PHYSIOLOGICAL CORRELATION – Iron Metabolism

Background: In *HFE*-related hereditary hemochromatosis, loss of functional HFE protein leads to aberrant hepatocellular sensing of plasma iron, with inappropriately low levels of hepcidin, diminished macrophage iron stores, and inappropriately greater duodenal iron absorption.

Problem: Draw a picture of the absorption of dietary iron by the duodenal enterocyte, and the role of both the intestine and the liver in causing hereditary hemochromatosis.

Colon

CLINICAL PHYSIOLOGICAL CHALLENGE – Constipation

Case: A 30 year-old mother of three pre-schoolers presents with a 3 month history of increasing constipation, by which she means three BM's per week, passing hard stools. There is no abdominal pain and no rectal bleeding. She is otherwise well.

Questions: Give the normal physiology of colonic transit. Classify the medications used to treat constipation. Give the safety of these medications during pregnancy and lactation.

CLINICAL PHYSIOLOGICAL CHALLENGE – Fecal incontinence

Case: A 60 year old mother of three children presents with fecal incontinence. There is no overflow diarrhea or urinary incontinence.

Questions: Give

- The physiology of defecation
- The approximate normal values of anorectal sphincter pressure and volumes of balloon distention to achieve rectal sensation.
- The tests used to investigate fecal incontinence, including sensory, motor and biomechanical function, as well as rectal capacity and composite sensory motor function.
- The medical, endoscopic and surgical treatments of fecal incontinence.

Miscellaneous Topics

CLINICAL PHYSIOLOGICAL CHALLENGE – CRC

Case: A 65 year old man presents with colorectal cancer (CRC). He wishes to know whether his family is at risk. Give the genes associated with CRC.

Answer:

- Three types of genes are induced in the transformation of normal to malignant cells:
 - Oncogenes (↑ cell growth)
 - Tumour suppressor genes (↓ growth)
 - DNA repair genes (↑ genome instability)

OVERVIEW of the GI TRACT

Luminal Anatomy of the GI Tract

- Definition of the GI Tract: “Just a long tube, with a couple of accessory secretory glands, with immune storage, digestive and absorptive functions”
- Function of the GI tract: to produce a sequential and coordinated secretory and absorptive response to a meal, and to help modulate food intake.

Functions

- Appetite and food intake
- Mouth and Saliva Glands
 - Chops up big bites of food (mastication)
 - Lubricates the smaller pieces of food with saliva
 - Begins the digestion of carbohydrates (salivary amylases)
 - Pushes the food and fluid into the upper esophagus (transfer phase of swallowing)
- Esophagus
 - Pushes food and fluid from the upper to the lower esophageal sphincter
 - The lower esophageal sphincter (LES) reduces the regurgitation of food and fluid from the stomach into the esophagus
- Stomach
 - Secretes HCl and pepsinogen, as well as gastrin and somatostatin, to aid in the digestion of carbohydrate, fat and protein
 - Partially destroys the bugs in food
 - Churns the food bits into even smaller pieces, and emulsifies lipids
 - Stores the partially digested and ground up “mush” until it is ready to be pushed by smooth muscle peristalsis into the duodenum
 - Secretes ghrelin, which has some longterm control over appetite and food intake
 - Turns off salivary secretion
 - Relaxes ileocecal valve
- Small Intestine
 - More digestion as well as absorption
 - Pushes remaining mixture of what is left of the meal and drink into the large bowel

- Releases hormones to stimulate secretions from pancreas, liver and gallbladder, as well as secreting hormones to reduce appetite and food intake
- Turns off gastric secretions
- Pancreas
 - Secretes enzymes to further digest carbohydrate, fat and proteins
 - Secretes HCO_3^- to neutralize gastric HCl in the duodenum
 - Secretes hormones which influence the metabolism of absorbed nutrients
- Liver
 - Synthesizes albumin, clotting factors, bile acids and cholesterol
 - Metabolizes bilirubin, drugs
 - Secretes bile, phospholipids, cholesterol, fluid
- Gallbladder
 - Stores bile acids and bilirubin until released into duodenum
 - Absorbs water to concentrate the bile acids
- Colon
 - Ferments the left-overs into a short chain fatty acids (acetic, butyric, propionic acids) and flatus
 - Absorbs water until feces are formed
 - Stores feces until the colon is ready to be evacuated
 - Helps prevent fecal incontinence

Digestion and absorption of macronutrients

Macronutrients	Digestion	Absorbed units
➤ Carbohydrates	○ Salivary/pancreatic amylase ○ AM disaccharides	○ Monosaccharides
○ Starch ○ Soluble/insoluble fiber ○ Disaccharides ○ Monosaccharides		
➤ Lipids	○ Lingual, gastric and pancreatic lipase	○ Fatty acids ○ Free cholesterol ○ FSV ○ Bile salts
○ Triglyceride ○ Cholesterol ○ Fat-soluble vitamins (FSV) ○ Bile salts		

Macronutrients		Digestion	Absorbed units
➤ Protein	○ Peptides	○ Gastric pepsinogen (pepsin) and pancreatic trypsinogen (trypsin) ○ AM dipeptides	○ Peptides (in minute amounts) ○ Small peptides (including di- and tripeptides) ○ Amino acids

Abbreviations: AM, enterocyte (apical) brush border membrane; FSV, fat soluble vitamins

Daily Intake: Calories, average baseline needs, 30 kcal/day; protein, 0.5 mg/kg; fluids, 1.5-2.5 L/day

Approximate daily volume output: Saliva 0.5 L/day; Stomach 1.0-1.5 L/day; in small intestine –8 L/day, ↑ bile; 0.5 L/day; colon 1-1.5 L/day; in feces

Daily Output in “poo” (stool, feces) about 200 g/day, depending on daily intake of fibre : stool consists of non-digested/non-absorbed food and fluids; intestinal bacteria.

Systems

- Integration
 - Digestion/absorption (assimilation = uptake across the brush border apical membrane [AM], and transfer across the basolateral mambrane [BM]), secretion, and motor activity (leading smooth muscle to peristalsis)
 - Neural, hormonal and paracrine responses, with sensor and transmission processes
 - Afferent and efferent components (turn “on” and turn “off”) the functions

When a function occurs at one site of the intestinal tract, the proximal portion becomes turned off, and the distal site is turned on (e.g., when the stomach is active, the salivary glands and esophagus “relax” their stimulated function, and the hepatopancreaticobiliary functions become ready to be stimulated.

- Neural
 - CNS (central nervous system; vagus nerve) and ENS (enteric nervous system; GI “mini-brain”) activate secretion and peristalsis through neuro transmitters.
 - Submucosal (Meissner’s) plexus): ENS of small and large intestine

- Myenteric (Auerbach's) plexus: ENS from esophagus to rectum in between the inner circular and outer longitudinal muscle layers
- Afferent sensory neurons: mechanoreceptors for smooth muscle tension, chemoreceptors (chemical, enteric toxins, pH, nutrients and osmoreceptors)
- Interneurons efferent secretomotor neurons (interneurons)
- Brain-gut axis modifies input from the parasympathetic nerves (vagus for the GI tract, except for the distal third of the colon), and from the autonomic ganglia (through the spinal cord, medulla and brain)
- Neurotransmitters
 - Excitatory motor neuron neurotransmitters (such as Ach [acetylcholine], enkephalins, VIP [vasoactive intestinal peptide], and NO [nitric oxide])
 - Inhibitory motor neuron neurotransmitters (such as serotonin [5-HT; 5-hydroxytryptamine], somatostatin and substance P)
- Hormonal
 - Mucosal receptors (mechanical, osmotic, chemical) act on neural pathways.
- Paracrine
 - Sensor cells release transmitters into adjacent effector cells.
- Parasympathetic
 - Pre- and post- ganglionic fibers (using Ach for pre ganglionic fibers, and for post-ganglionic fibers, as well as other neurotransmitters).
 - Efferent fibers pass to the medulla.
- Sympathetic
 - Pre-ganglionic fibers and post-ganglionic neurons pass to, into post-ganglionic sympathetic fibers which synapse on either ENS or on effector cells.

CONTROL of FOOD INTAKE

Control of Food Intake

- To reach the stage of following a hamburger, fries and shake through the gastrointestinal (GI) tract, we must first have the desire to eat and the willingness to ingest this high fat, high carbohydrate and high calorie meal. This control of food intake is a complex and integrated process, and only an overview will be given here.

Useful Background: Terms used to describe the balance of energy expenditure

- RMR – Resting metabolic rate (~2,100 kcal/day in a 70-kg adult)
- AREE – Activity-related energy expenditure
- NEAT – Non-exercise-associated thermogenesis (e.g. typing, looking around: varies 3-to 10- fold between persons → about 500 kcal/day)
- DIT – Diet-induced thermogenesis – about 10% of daily energy expenditure

Weight = energy in – energy out

Weight gain occurs from positive energy balance (in > out)

CLINICAL PHYSIOLOGICAL CHALLENGE

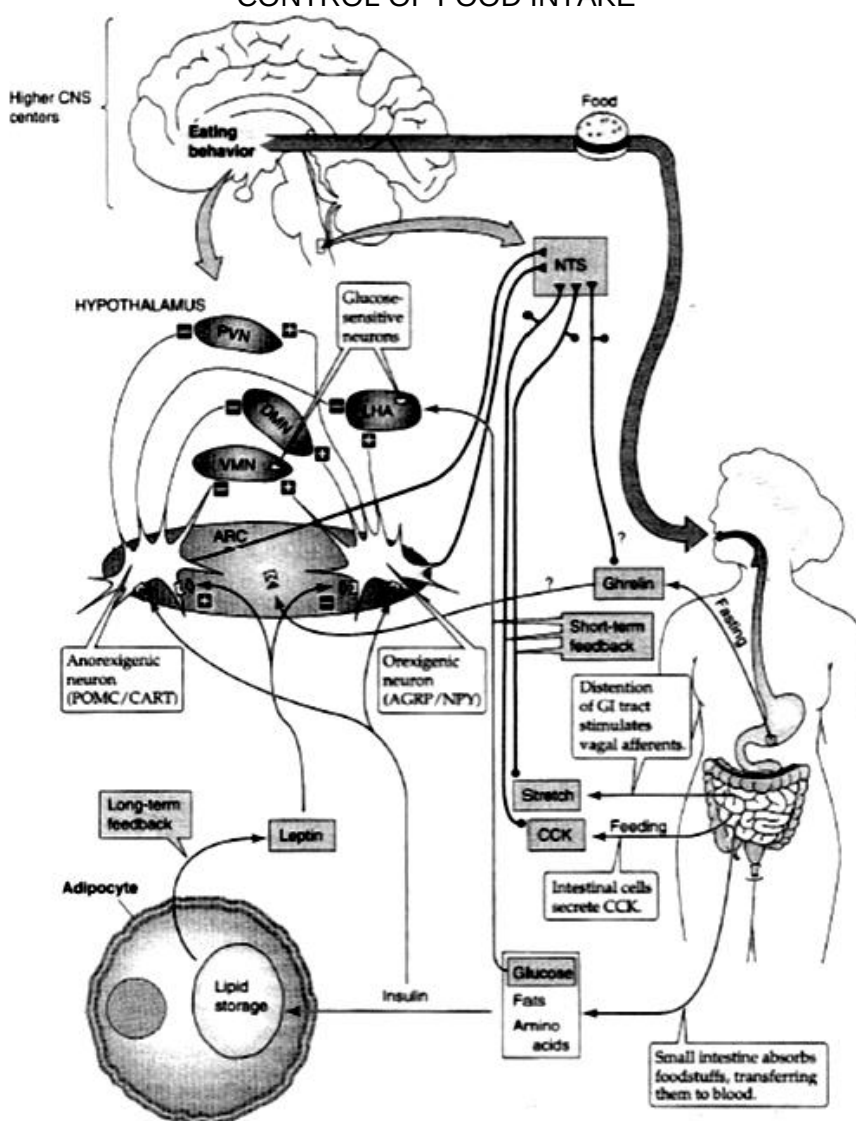
Case: There is a world-wide epidemic in the development of increased BMI (aka obesity), and with this the onset of numerous weight-associated diseases. Your patient is an educated, sophisticated 45 year old CEO. She has undertaken a literature search to learn more about the pro's and con's of dieting versus exercise. She has already consulted an exercise physiologist, and now consults you to learn about how she can modify her food intake in order to loose weight.

Question: What are the mechanisms involved in the control of food intake?

→ In your answer, give the role of each of the following:

11. Mouth and GI tract
12. Adipocyte, Leptin, Insulin, Ghrelin, Incretins
13. POMC – secreting neurons (pro – opiomelanocortin)
14. ARC (arcuate nucleus)
15. PVN (paraventricular nucleus), LHN (lateral hypothalamic area hunger centre)
16. NTS (nuclear tractus solitaires)
17. CCK and GLP-1
18. PYY
19. Orexigenic pathyways
20. Anorexigenic pathways

CONTROL OF FOOD INTAKE



Abbreviations: AGRP, agouti-related protein; CCK, cholecystokinin; DMN, dorsomedial hypothalamic nucleus; LHA, lateral hypothalamic area; NTS, nucleus tractus solitarius; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; VMN, venteromedial nucleus

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Figure 48.9, page 1041, Ninth Edition, 2010

Networks Involved in the Control of Food Intake

- Mouth- oropharyngeal reflexes are stimulated by chewing and swallowing, and may reduce food intake after a certain threshold.
- GI tract
 - A. Stomach - releases leptin and ghrelin
 - B. Small intestine - releases PYY, CCK, GLP-1
 - C. Pancreas - releases insulin
- Leptin and Adipocytes
 - Leptin tells the brain how much fat is stored.
 - Plasma leptin concentration increases as the mass of the adipocyte tissue increases.
 - Leptin is a 17-kDa protein, made mostly in adipocytes.
 - Leptin binds to its receptor Ob-r.
 - Ob-r is a tyrosine kinase- associated leptin receptor that signals through JAK-2 and STAT.
 - Leptin and insulin are satiety-producing (anorexigenic)
 - A deficiency of Ob-r leads to leptin resistance.
 - $T_{1/2}$ of leptin is about 75 min; fasting or short term changes in food intake have little effect on leptin concentrations.
 - Leptin from the stomach and insulin from the pancreas inhibit the neuropeptide Y (NPY) and the agouti-related protein (AGRP) neurons in ARC.
- Insulin
 - Stimulation of arc neurons containing
 - POMC (pro-opiomelanocortin)
 - CART (cocaine and amphetamine regulated transcript neurons)
 - Insulin concentration changes rapidly in response to food intake, and is more of a short-term regulator of ARC, while leptin is more long-term.

- Hypoglycemia
 - stimulates glucose- sensitive neurons in lateral hypothalamic area hunger (feeding) centre (LHA)
 - inhibits glucose- sensitive neurons in ventromedial nucleus satiety centre (VMN)
 - activates orexin- containing neurons in lateral hypothalamic area hunger [feeding] centre (LHA)
- Leptin and insulin stimulate the ARC neurons containing POMC (pro-opiomelanocortin) and the cocaine and amphetamine regulated transcript (CART) neurons.

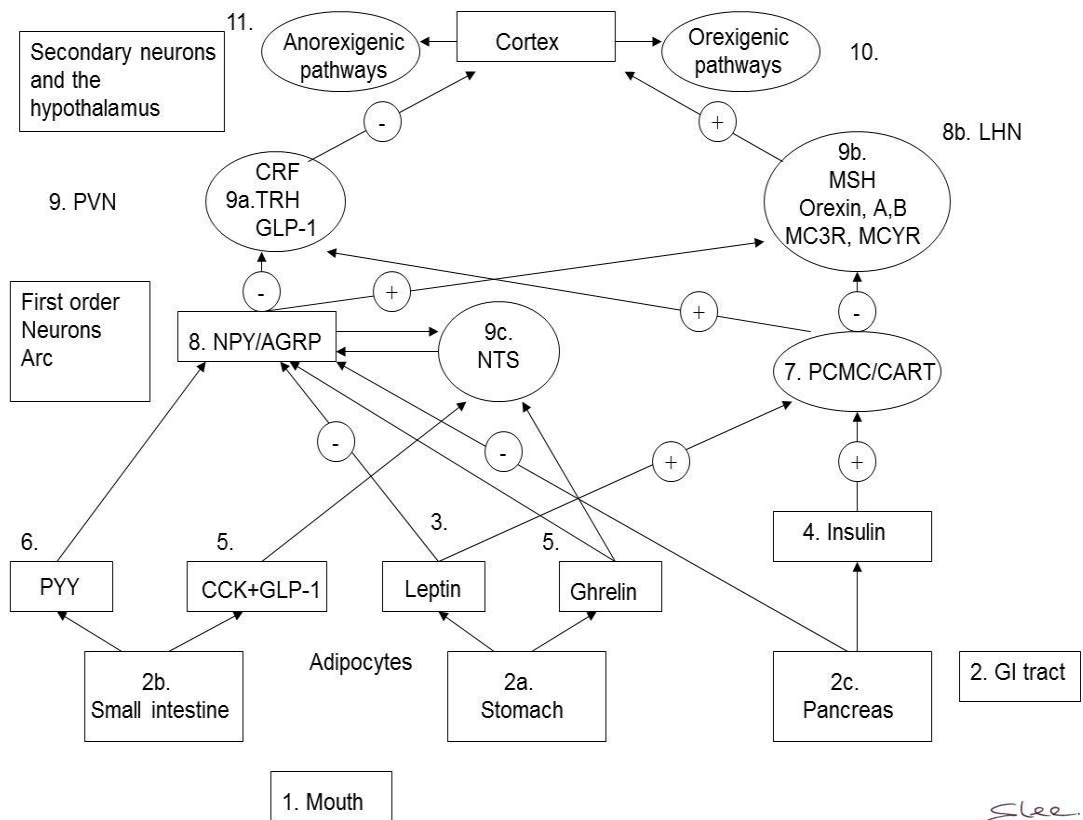
SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q: Give 5 GI conditions in which there has been demonstrated to be superior clinical outcome with the use of parenteral nutrition orders

A.

- Pre- but not post-operative nutritional support given to surgical patients (including gastric and colorectal cancer ↓ morbidity by 35%, as well as ↓ mortality (by a lesser amount)
- Persons with decompensated alcoholic liver disease or alcoholic hepatitis have ↓ mortality & mortality, as well as faster recovery, when nutritional support is provided with enteral or parental nutrition.
- Patients with acute pancreatitis do better with nutritional support
- Curiously, persons with IBD treated with TPN have a worse outcome
- Cancer patients receiving radiotherapy have a superior quality of life with nutrition support
- Tumour obstruction of bowel – PN is beneficial
- Bone marrow transplantation associated mucositis (may have associated diarrhea) – PN is beneficial

NETWORKS INVOLVED IN THE CONTROL OF FOOD INTAKE



Abbreviations: AGRP, agouti-related protein; ARC, arcuate nucleus of the hypothalamus; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CNS, central nervous system; CRF, corticotrophin releasing factor; GLP-1, glucagon-like peptide-1; LHA, lateral hypothalamic area; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; NS, nervous system; NTS, nucleus tractus solitaries; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus of the hypothalamus; PYY, peptide YY3-36; TRH, thyrotropin-releasing hormone; VMN, ventromedial nucleus satiety centre

Adapted from: Foxx-Orenstein AE. 2008; *ACG Annual Postgraduate Course Book*: page 148. Quoted in *GI Practice Review*, 2010; *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 48.9, page 1041.

➤ Ghrelin

- Food releases ghrelin, glucagon, GLP-1 (glucagon-like peptide-1), gastrin-releasing peptide (GRP), SS, peptide YY (PYY), and CCK* (cholecystokinin).
- These cause short-term ↓ intake.
- Gastric ghrelin is the only GI hormone which stimulates food intake.
- Ghrelin acts on both the brainstem solitary nucleus (NTS) as well as on the hypothalamus.
- Ghrelin released from the gastric mucosa from the presence of food binds to GHSR in arcuate nucleus (ARC) and vagal afferents to ↓ food intake.
- Gastric leptin, small intestinal PYY, CCK and GLP-1 as well as pancreatic insulin lower food intake.
- Small intestinal PYY acts on ARC, whereas small intestinal CCK and GLP-1 act on NTS., CNS networks.

➤ Incretins

- GLP and GIP are incretins, GI peptides which stimulate the entero-insular axis to release insulin from the pancreatic beta cells (enhance glucose-stimulated insulin release).
- Other incretins include GRP (gastrin releasing peptide), gastrin in the presence of amino acids, CCK (which enhances amino acid-stimulated insulin release), motilin, VIP (vasoactive intestinal peptide) and PACAP (pituitary adenylate cyclase activating peptide).
- CB-1/CB-2 binds endocannabinoids, endogenously produced arachidonic acid derivatives.
- While CCK-RF stimulates the ECL cell to release CCF, CCK-RF reduces pancreatic secretion by negative feedback.
- Absorbed glucose stimulates the secretion of GLP-1 and GIP (glucose-dependent insulintropic peptide).

- The functions of GLP-1 are:
 - GLP-1 acts on GLP-1 receptors (in the periventricular nucleus [PVN], dorsal medial hypothalamus [DMH] and the arcuate nucleus [ARC] of the hypothalamus).
 - Stimulates insulin secretion
 - Delays gastric emptying
 - ↑ satiety (↓ appetite), ↓ food intake
 - The GI peptide amylin suppresses the secretion of glucagon and thereby reduces hepatic gluconeogenesis.
 - Amylin CCK and secretin ↓ gastric emptying, so ↓ carbohydrate reaches the small intestine to be digested and absorbed.
- POMC-secreting neurons
- POMC / CART and NPY / AGRP comprise the ARC.
 - The POMC-secreting neurons have receptors for leptin and for insulin.
 - When stimulated by leptin or insulin, these neurons produce either the neuropeptide POMC (pro-opiomelanocortin) from one class of neurons, or neuropeptide Y (NPY) and agouti-related protein (AGRP) from another class of neurons.
 - From the synapses of POMC neurons, a cleavage product of POMC is released, α -MSH (melanocortin α - melanocyte – stimulating hormone).
 - α -MSH binds to second – order neurons which contain MC3R and MC4R melanocortin receptors.
 - Stimulation of MC3R/MC4R by α -MSH from POMC is anorexigenic (↓ food intake and ↑ satiety), as well as increases energy expenditure by way of activating descending sympathetic pathways.
 - The first order POMC neurons also synthesize and release CART (cocaine-amphetamine-related transcript), which is also anorexigenic.

- NPY / AGRP are also first order neurons
 - ARC has both inhibitory and stimulating influences on PVN and LHN.
 - The NPY/AGRP neurons activate the NPY receptors Y1R/Y5R (GPCRs, cannabinoid receptors) on secondary neurons, leading to ↑ food intake.
 - NPY inhibits PVN.
 - AGRP binds to MC4R melanocortin receptors on the secondary neurons of the POMC pathway, reducing the anorexigenic effect of α -MSH, thereby producing an orexigenic effect.
 - AP in the cortex is stimulated by the corticotrophin releasing factor (CRF), thyrotropin-releasing hormone (TRH), and glucagon-like peptide-1 (GLP)-1 containing second order neurons in PVN inhibit the anorexigenic pathways to ↑ satiety ↓ food intake.
 - Cortical OP is stimulated by melanocyte-stimulating hormone (MSH) as well as orexin A and B in LHN.
 - CB-1/CB-2
 - The GPCRs are cannabinoid receptors in the basal hypothalamus, other parts of the brain, vagal afferents, as well as in peripheral tissue.
- PVN, LHN and NTS: secondary neurons in the hypothalamus
 - The PVN positively influences the cortical anorexigenic pathways (AP), and the LHN positively influences the cortical orexigenic pathways (OP).
 - Reacts to
 - Psychosocial factors
 - Social norm
 - Cortical control
 - Environmental factors
 - LHN
 - Lateral hypothalamic area hunger (feeding) centre
 - NPY/AGRP neurons stimulate and POMC neurons inhibit the secondary neurons producing the orexigenic peptides melanin-concentrating hormone (MCH) and orexins A and B

- VMN – Venteromedial nucleus satiety centre
- DMN – Dorsomedial hypothalamic nucleus
- PVN – Paraventricular nucleus
 - Neurons project to the brainstem and to the cerebral cortex
- NTS – nucleus tractus solitaries a second order neuron in the hypothalamus
- Nucleus tractus solitaries (NTS) receives input from PVN, and integrates sensory information from the viscera by way of vagal afferents
- Distention triggers vagal afferents, which act through the nucleus tractus

CLINICAL PHYSIOLOGICAL CHALLENGE – meal size of a person with obesity

Case: Thinking back to the previous case, what are the factors which increase or decrease the size of meals?

- Factors which increase meal size (orexigenic effect)
 - Ghrelin stimulates NTS in brainstem.
 - CCK and secretin are released from ECL cells by intraluminal releasing factors (e.g., CCK releasing factor [CCK-RF]).
 - With food intake, CCK-RF stimulates CCK release into the blood. As the food stimulus lessens, trypsin in the intestinal lumen digests CCK-RF, and the release of CCK is diminished.
- Factors which reduce meal size (anorexigenic effect)
 - Cholecystokinin (CCK)
 - Glucagon-like peptide-2 (GLP-1)
 - Peptide tyrosine (PYY₃₋₃₆)
 - Gastrin releasing peptide (GRP)
 - Amylin
 - Apolipoprotein A-IV
 - Somatostatin
 - Leptin

Useful background: Q&As

Q. Give the physiological effects of leptin and ghrelin.

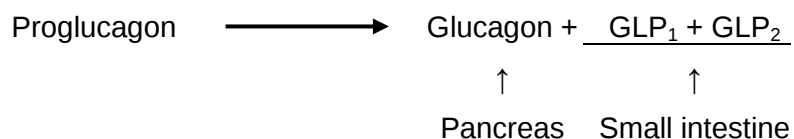
- Leptin
 - Source
 - Adipocytes, lesser amounts in gastric chief cells and placenta, as well as in breast milk
 - Composition
 - 167- amino acid protein
 - Receptor
 - 5 different forms
 - Blood brain barrier – may be defective in obesity
 - Hypothalamus – activated JAK stat (Janis kinase signal transduction and translation system)
 - Action
 - Reduces food intake
 - ↓ NPY neuropeptide Y, a transmitter in central and peripheral nervous system (PNS)
 - ↑ α -MSH (α -melanocyte – stimulating hormone)
- Ghrelin (GHR)
 - Source
 - Gastric fundic P/D₁ cells; minute amounts in small intestine, pancreas, pituitary, kidney, and placenta
 - Composition
 - 28 – amino acid peptide
 - Receptor
 - GHR (growth hormone [GH] secretagogue receptor)
 - Action
 - Pre-meal and post-meal decrease in GHR concentration in blood
 - ↑ GH secretion
 - ↑ GHR levels before meals (fasting)
 - When BMI is low, ↑ GHR
 - Signal to begin eating
 - Activates NPY and agouti – related protein producing-neurons in arcuate nucleus of hypothalamus
 - Acts on vagus nerve to ↑ gastric contraction

- Clinical
 - Bariatric gastric bypass surgery removes the normal premeal increase in ghrelin, thereby contributing to the desired weight loss
 - Prader – Willi syndrome (congenital obesity growth hormone deficiency, hypogonadism) ↑ GHR in circulation that fails to fall after eating, resulting in hyperphagia and ↑ BMI

Q. Numerous gastrointestinal peptides (GIPs) decrease food intake. Which of the following increases food intake?

- A.
- a) CCK, GLP-1
 - b) PYY, GRP
 - c) Amylin, apoA-iv
 - d) Somatostatin, leptin
 - * e) Ghrelin

Q. Amylin (islet amyloid peptide) is a 37-amino acid peptide secreted from the pancreatic islet cells with insulin. The action of amylin is to ↓ glucagon release, and along with CCK and secretin, to slow gastric emptying.



This helps to regulate postprandial blood glucose concentrations [GC], GI peptides also regulate postprandial [GCI] by stimulating insulin release.

- In this context, what is the enteroinsular axis, and list 5 incretins.
- A.
- Definition: the enteroinsular axis and incretins are the GI peptides which stimulate pancreatic islet cell insulin release, and thereby play a role in glucose homeostasis.
 - GLP-1 and GIP (glucose-dependent insulinotropic peptide) are the most important incretins. Others include
 - CCK
 - Gastrin

- GRP (gastrin releasing peptide)
- Motilin
- PACAP (pituitary adenylate cyclase- activating peptide)
- VIP (vasoactive intestinal peptide)

Note: while amylin and secretin regulate postprandial blood glucose concentrations by inhibiting the release of glucagon (amylin), as well as by slowing gastric emptying (amylin, secretin), they are not considered to be incretins because they do not stimulate the release of insulin.

XX

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. Incretins are responsible for about half of the postprandial release of insulin. The major incretins are GLP-1 and GIP. What role do these two incretins play in type II diabetes mellitus?

- A.
- GIP – normal secretion but ↓ response
 - GLP – ↓ secretion
- XX

Useful Background: Calculations of Total Energy Expenditure

$$TEE = REE + PAEE + TEF$$

Abbreviation: PAEE, physical activity energy expenditure (20% of TEE); REE, resting energy expenditure (70% of TEE); TEE, total energy expenditure; TEF, thermal effect of feeding (10% of TEE)

Starvation

Useful background: Q&As

Q1. Postoperatively a patient is kept NPO and is hydrated with intravenous normal saline.

- Give the compensatory mechanisms which are involved to reduce the impact of developing deficiencies in energy and/ or protein when a patient is starved.

A1.

- First 24 hr use of ,
 - Circulating nutrients – glucose, fatty acids (FAs) , triglycerides) 1200 kcal

- Stores – liver & muscle glycogen → ↑ glycogenolysis → ↑ glucose
 - Liver metabolism - ↓ glucose production & oxidation
 - Whole body - ↑ lipolysis → ↑ FAs, ↑ ketone bodies
- Next several days
- Oxidation of protein (proteolysis):
 - glucogenic amino acids (alanine, glutamine) → ↑ deamination - ↑ renal production of glucose [especially for brain & blood cells; (gluconeogenesis)]
- Up to 2 wk of starvation
- Adipose tissue
 - ↑ lipolysis → FA, from ↑ shift of AA from somatic (muscle) to visceral organ compartment eventual loss of visceral protein
 - ↓ insulin
 - ↑ epinephrine
 - ↑ adipocyte sensitivity to catecholamines
 - Liver
 - ketogenesis
 - ↑ FA from ↑ lipolysis (see above)
 - ↑ glucagon/ insulin
 - ↑ ketone bodies use by brain, in place of glucose
 - reduces brain need for glucose, and need for oxidation of protein
 - Heart, kidney, skeletal muscle - ↑ use of FAs & ketone bodies
 - Bone marrow, renal medulla, peripheral nerves
 - ↑ anaerobic glycolysis → ↑ pyruvate (P) & lactate (L) → ↑ glucose production of from P&L via the Cori cycle
 - ↑ Sympathetic nervous system (SNS) activity
 - Thyroid - ↑ inactive hormone (net effect: TG → FA → glucose)

- Physical activity ↓ from
 - ↓ active thyroid hormone
 - ↓ SNS activity
- After 2 wk of starvation
 - Organs shrink
 - Limit of TG stores reached (lethal depletion: 70% to 95%)
 - ↑ muscle protein breakdown (lethal depletion: 30% to 50%)
 - ↓ BMI (lethal reduction: < 13 kg/m² (males), < 11 kg/m² (females))
 - Plateau reached in adaptive processes
 - Kidney
 - ↓ urea nitrogen (N) production & excretion (1 g of urinary N arises from the breakdown of 30 g of protein)
 - ↓ urine output
 - Death

Q2: Give two compensatory metabolic mechanisms blunted in obesity, and thereby represents an adaptation which slows the effect of fasting on weight reduction.

A2:

- ↑ lipolysis
- ↓ glucose production

Protein – Energy Malnutrition (PEM)

- Importance of assessment of nutritional status
 - PEM is associated with poor clinical outcomes
 - Two useful tools
 - SGA (subjective global assessment)
 - MNA (mini-nutritional assessment)

➤ Primary PEM

- ↓ intake of protein ± calories, or
- ↓ intake of good quality protein (inadequate essential amino acids)

➤ Secondary PEM

- ↑ systemic inflammatory response (eg IBD) → ↑ IL-1, TNF- α , interferon & IL-6
- ↑ protein catabolism
- ↑ REE

➤ PEM in the presence of active inflammation

- Even with nutritional support, lean body mass (including muscle mass) will not correct until the systemic inflammatory response from associated inflammation is corrected.
- If a gain in weight occurs in the person with secondary PEM, before associated inflammation is treated, the weight gain is mostly fluid (edema) and fat

➤ Special consideration: cancer wasting syndrome

- PEM is accelerated by the production of proteolysis – and lipid – metabolizing factors
- PEM must be corrected slowly, to avoid (the refeeding syndrome)
 - If glucose is fed rapidly, insulin is released, phosphate is rapidly taken up into cells, the serum PO_4^- falls, and complications develop:
 - Neurological (seizures, paresthesias, hyperosmolar coma) and cardiovascular (CCF, death)
 - GI – diarrhea, death
 - RBC fail to release O_2 normally – VT
 - Acute thiamine deficiency (wet beriberi) initiation of parenteral nutrition, including peripheral as well as total parenteral nutrition.

- The cells in PEM are depleted of K^+ & Mg^{2+} , and refeeding with glucose/ AAs shifts these back into cells, and may lead to serious cardiovascular adverse effects (prolonged QT interval, ventricular tachycardia (VT))
 - Remember that the refeeding syndrome may occur with
- Predigested monomeric or oligomeric elemental or semielemental diets are not superior to polymeric diets or whole food
 - In order for any hypocalcemia to be fully corrected, it may be necessary to correct any associated body depletion of Mg^{2+} (best assessed from urinary levels after IV infusion rather than from serum concentrations)

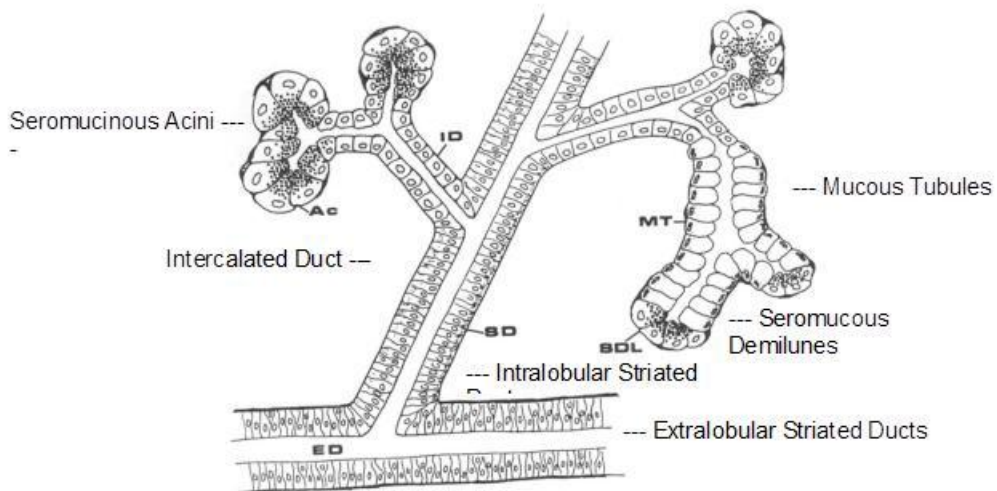
MOUTH and SALIVARY GLANDS

THE SECRETORY ENDPieces AND DUCT SYSTEM OF THE HUMAN SUBMANDIBULAR GLAND

CLINICAL PHYSIOLOGICAL CHALLENGE – salivary secretion

Background: Salivary acinar cells secrete KHCO_3 and absorb NaCl . The apical (luminal) membrane contains a Na^+/H^+ , $\text{Cl}^-/\text{HCO}_3^-$ and a H^+/K^+ exchanger as well as epithelial Na^+ channels (ENaC) and CFTR (cystic fibrosis transmembrane regulator). The basolateral membrane contains a Na^+/H^+ exchanger, NaHCO_3 cotransporter, Na^+/K^+ ATPase, as well as K^+ channels and non-CFTR Cl^- channels.

Problem: With these components, draw a diagram which depicts the steps in the salivary secretion of fluid and electrolytes.



Structure

- The duct cells alter the composition of the secretion from the acinar cells
- The duct cells have many mitochondria, and their basal portion is striated

- The tightness of the tight junction (TJs) of the salivary glands lead to their low permeability to water, and to hypotonic secretion at low flow rates
- Acinar cells of the parotid gland secrete a serous watery fluid which contains amylase activity
- Sublingual glands secrete a highly glycosylated mucin glycoprotein
- The submandibular glands secrete both serous and mucinous fluid from separate serous- and mucus- acinar units. Highly glycosylated proline-rich proteins are also secreted in both the serous- and the mucous- acinar units.

Function

- Grinding of food (mastication) and lubrication with saliva
- Some digestion of carbohydrate in the mouth through lingual amylase
- Secretion of saliva

Gland	Secretion	
	Mucin	Serous
Parotid	-	+
Sublingual	+	-
Submandibular	+	+

- AM
 - NHE (Na^+ / H^+ exchanger)
 - ENaCs (epithelial Na^+ channels)
 - CFTR (cystic fibrosis transmembrane receptor)
 - HKE (H^+ - K^+ exchanger)
- BM
 - CC (Cl^- channel)
 - NaHCO_3E (Na^+ / HCO_3^- exchanger)
 - Na^+ - K^+ ATPase
 - KC (K^+ channel)

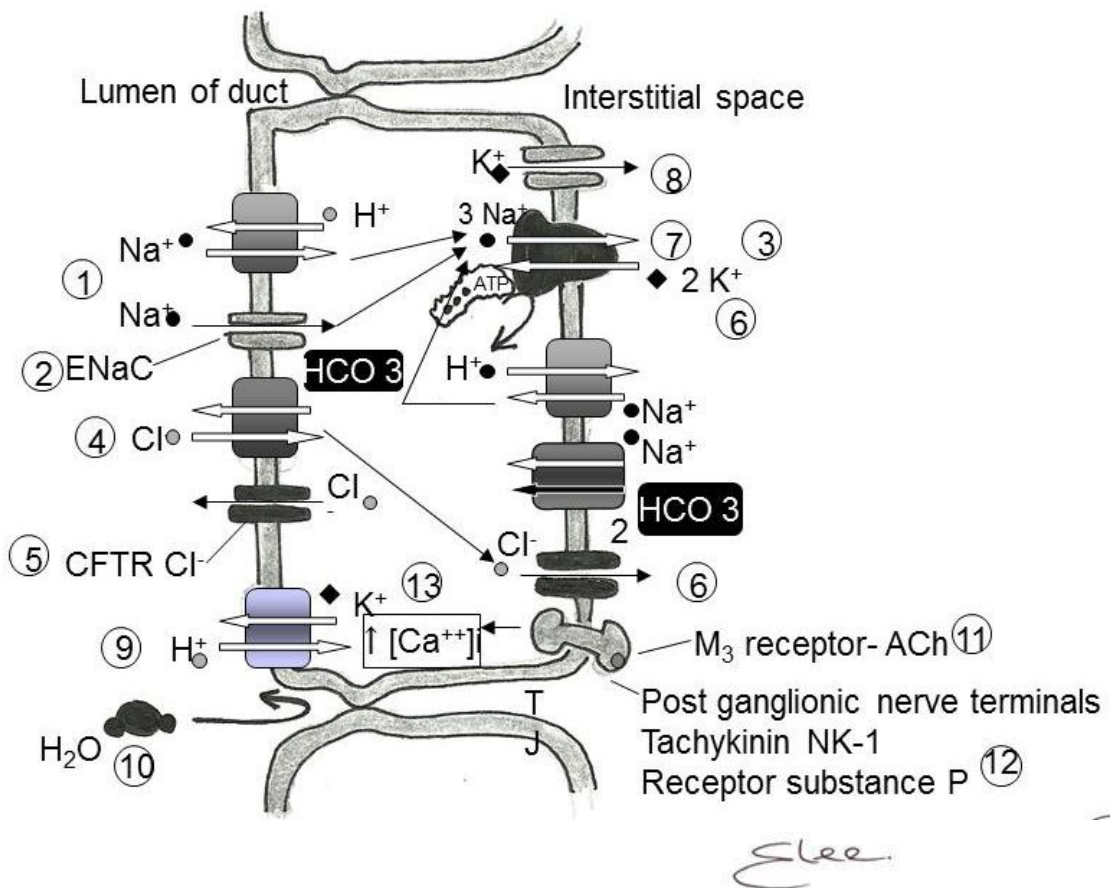
➤ Na^+

- In
 - 1) Na^+ enters the salivary cell from the lumen of the duct across the apical membrane (AM) ENaCs (epithelial Na^+ channels) and the Na^+ / H^+ exchanger (NHE)
- Out
 - 2) The intracellular Na^+ concentration acts through the ubiquitin-protein ligase (U-PL) to provide feedback inhibition on ENaC, reducing further Na^+ entry into the cell across AM.
 - 3) Na^+ leaves the salivary cell from the Na^+ - K^+ pump

➤ Cl^-

- In
 - 4) Cl^- enters the salivary cell by the AM Cl^- / HCO_3^- exchanger.
- Out
 - 5) CFTR secretes Cl^- out of the enterocyte across the AM.
 - 6) The non-CFTR channels in the basal membrane (BM) provide another pathway for the exit of Cl^- from the enterocyte.

STEPS IN THE SALIVARY SECRETION OF FLUID AND ELECTROLYTES



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 43-10, page 928,

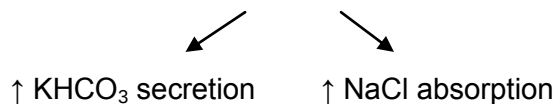
➤ K^+

- In
 - 7) K^+ enters the salivary cell by the BM Na^+ - K^+ exchanger.
 - 8) K^+ possibly exits by a BM K^+ -channel.

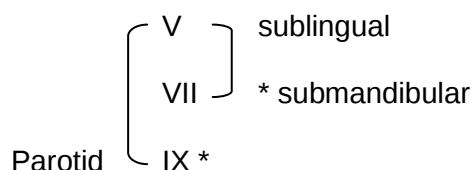
- Out
 - 9) In the AM, K^+ is exchanged for H^+ , with K^+ leaving the cell, and H^+ entering
 - The K^+ secreted by the H^+/K^+ exchanger binds to the HCO_3^- secreted by the AM Cl^-/HCO_3^- exchanger.
- Water
 - 10) The tightness of the tight junctions (TJs) leads to low permeability of the AM to water, and thereby to the hypotonic secretion of saliva at low flow rates

- Stimulation

- Preganglionic parasympathetic fibers (CN V, VII, IX) → postganglionic nerve terminals → Ach → duct BM M3 receptors → $\uparrow [Ca^{2+}]$



- The sublingual and submandibular salivary glands are supplied with preganglionic parasympathetic fibers in cranial nerve (CN) VII and less so in CN V.
- The parotid gland receives preganglionic parasympathetic fibers mainly in CN IX, and less so through CN V.



- 11) Parasympathetic stimulation releases Ach from postganglionic nerve terminals, which acts on salivary duct cell BM M3 receptors to increase intracellular Ca^{2+}
- 12) Substance P acts on the BM tachykinin NK-1 receptor to increase fluid secretion through the Ca^{2+} signaling pathway

- 13) $\uparrow[\text{Ca}^{2+}]_i$ enhances fluid secretion by activating the Ca^{2+} - signaling pathways to increase KHCO_3 secretion and NaCl absorption.

Regulation of Salivary Secretion

CLINICAL PHYSIOLOGICAL CHALLENGE – Salivary secretion

Background: The salivary gland is innervated by the parasympathetic and sympathetic nervous systems.

Problem: Provide the explanation for the development of xerostomia in some persons with Sjogren's syndrome, or treated with anticholinergics.

➤ Sympathetic system

- Superior cervical ganglia postganglionic sympathetic fibers → norepinephrine (Nor') → $\uparrow$ blood flow
 - $\uparrow$ salivary adrenergic receptors and Ca^{2+} signalling pathways
 - $\uparrow$ CFTR - $\uparrow\uparrow$ NaCl absorption
 - $\uparrow$ amylase, ribonucleases
 - $\uparrow$ stimulation of myoepithelial cells - $\downarrow$ resistance to flow - $\uparrow$ salivary flow
- Postganglionic sympathetic fibers from the superior cervical ganglia reach the parotid, sublingual and submandibular salivary glands in the blood vessels that supply these glands.
- Sympathetic stimulation increases blood flow to these glands, and this enhanced salivary gland blood flow increases salivary gland secretion.
- Sympathetic stimulation releases norepinephrine from sympathetic nerve terminals, norepinephrine released from the sympathetic nerve terminals stimulates CFTR, and thereby increases NaCl absorption.
- Because the cholinergic stimulation is more limited than the adrenergic, NaCl reabsorption may exceed KHCO_3 secretion, and salivary secretion falls, causing a dry mouth (xerostomia).

- Norepinephrine (Nor') released through the sympathetic nerve terminals also acts through adrenergic receptors and the Ca^{2+} signalling pathway.
- This effect of norepinephrine on adrenergic receptors and the Ca^{2+} signalling pathway cause the salivary duct cells to secrete amylase and ribonucleases into the mouth, using the cAMP pathway sympathetic control.
- IgA secretion into the mouth by endocytosis is facilitated by the secretory component.
- Secretion of IgA also occurs through BM polymeric IgA receptors
- When the stellate-shaped myoepithelial cells in the salivary gland acinar and intercalated duct cells are stimulated by the sympathetic system, the resistance to salivary flow is reduced, and salivary gland flow increases.

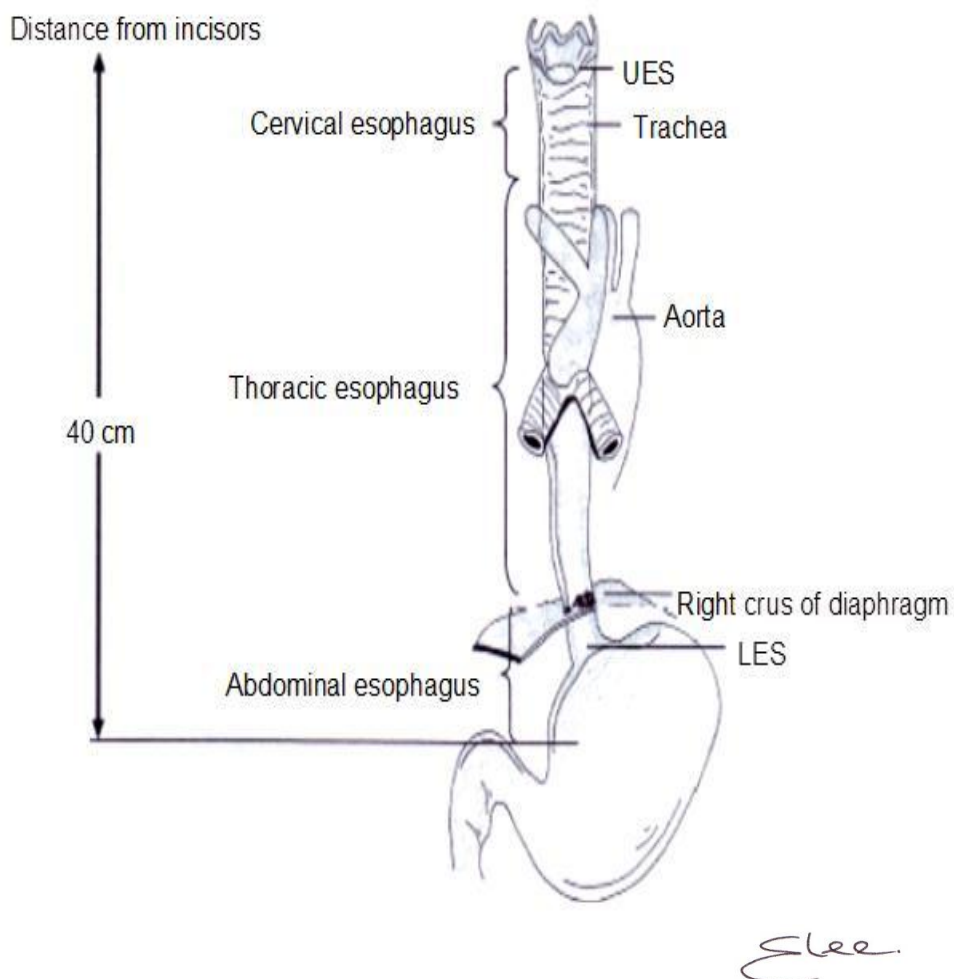
CLINICAL PHYSIOLOGICAL CHALLENGE – Xerostomia

Background: The salivary gland is innervated by the parasympathetic and sympathetic nervous systems.

Problem: Provide the explanation for the development of xerostomia in some persons with Sjogren's syndrome, or treated with anticholinergics.

ESOPHAGUS

Gross Anatomy of Esophagus



Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*.
Figure 31-1, page 552, Ninth Edition, 2010.

Main Diseases

- Motility disorders(scleroderma, achalasia, diffuse esophageal spasm, hypertensive [“nutcracker”] esophagus)
- Gastroesophageal Reflux Disease (GERD)

Functions

- To facilitate the passage of food and fluids from mouth to stomach (transit)
- To prevent the regurgitation of gastric contents back up the esophagus (gastroesophageal reflux)

Structure

- Hollow muscular tube, functionally closed at the upper (pharyngeal) end by the upper esophageal sphincter (UES), and at the lower (gastric) end by the lower esophageal sphincter (LES).
- The UES is a high pressure area formed from the tonic contraction of the striated cricopharyngeal and the caudal fibers of the inferior pharyngeal constrictor muscles.
- The muscle of the proximal (cervical) 30% of the esophagus is also striated, and the distal 70% is smooth muscle.
- The distal portion of this smooth muscle thickens at or just below the diaphragmatic hiatus to form the LES.
- The LES has circular “clasp” fibers on the gastric lesser curvature side of this junction between the esophagus and stomach; on the greater curvature side of the LES the “sling-like” muscle fibers form the long oblique gastric muscle fibers.
- The venous blood drainage of the lower esophagus involves the azygous and the portal systems.
- If pressure is increased in the portal circulation, this pressure is transmitted through the left gastric vein, and the submucosal venous plexus enlarges. If the portal pressure continues to increase (portal hypertension, such as hepatic cirrhosis), esophageal varices result.

- If the portal pressure exceeds 12 mm Hg, these esophageal varices may burst, leading to life-threatening bleeding (variceal upper GI bleeding).
- The histology of the esophagus varies slightly from the usual pattern of the GI tract:
 - Stratified squamous epithelium down to the LES, where there is columnar epithelium at the point where the esophagus meets the stomach.
 - The outer layer of the wall of the esophagus is only a thin layer of connective tissue, rather than the distinct serosal layer, so that the esophagus lacks this protective layer and is more prone to perforation.

CLINICAL PHYSIOLOGICAL CHALLENGE – GERD: “Reflux” disease

Case: A 45 year old man with an increased BMI of 29 began to develop severe retrosternal burning discomfort and acid regurgitation when his new –onset hypertension was treated with a calcium channel blocker. His symptoms of gastroesophageal reflux disease (GERD) were worsened by bending forward after meals, and by eating chocolate.

Questions: What is the physiology of GERD?

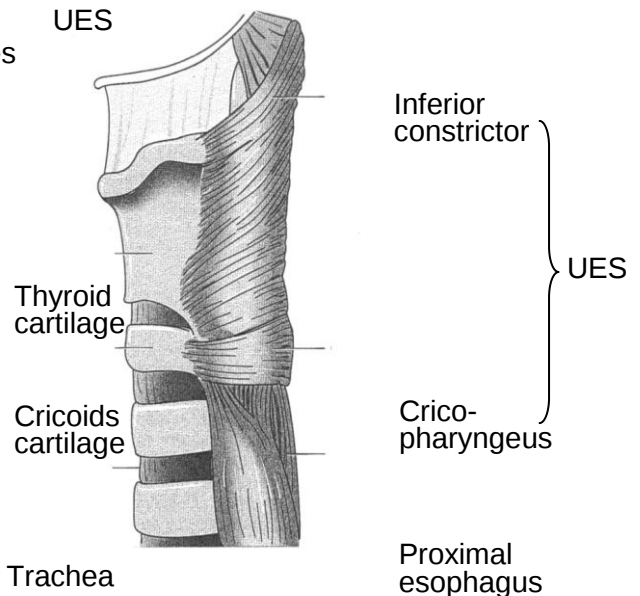
→ In giving your answer, please include the manometric pressure valves of the upper (UES) and lower esophageal sphincter (LES), as well as the characteristics of the peristaltic waves of the esophageal body

- Structure and function of esophagus
- Tone and relaxation of LES
- Peripheral and central pathways mediating transient lower esophageal sphincter relaxations
- Conditions associated with GERD
- Maintenance of integrity of esophageal mucosal membrane

➤ UES

Normal Esophageal Manometric Values

- Resting Pressure 30-120 mm Hg
- Residual Pressure after swallowing < 8 mm Hg
- Coordination with swallow Yes

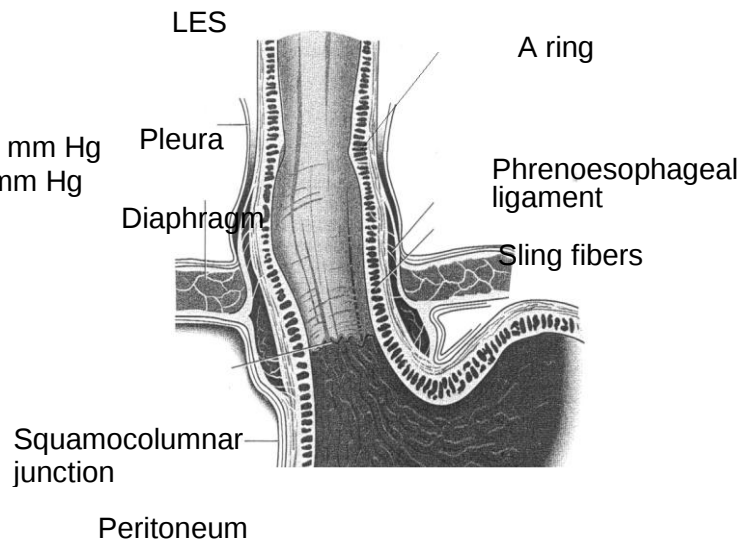


➤ Esophageal Body

Contraction: Peristaltic	> 80%
Simultaneous	< 20%
Non-conducted waves	0%
Mean contraction amplitude	30-180 mm Hg
Duration	< 5.8 secs
Low amplitude contractions	< 30%
High amplitude contractions	0%

➤ LES

- Resting Pressure 13-43 mm Hg
- Residual Pressure after swallow < 13 mm Hg
- Hiatus hernia No



Abbreviations: LES, lower esophageal sphincter; UES, upper esophageal sphincter

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 31-1, page 552, Ninth Edition, 2010

Lower Esophageal Sphincter (UES and LES)

- The tonic resting tone of the LES is due to the properties of the smooth muscle fibers which create the LES (ie myogenic factors).

Competence of the LES

➤ Resting Pressure

- The inherent property of the smooth muscle at the junction between the esophagus and the stomach forms the tonic contraction (myogenic) which results in the high-pressure LES zone.
- Between swallows, the pressure in the LES is between 10 to 35 mm Hg.
- On swallowing, the vagal efferent fibers synapse on inhibitory neurons in the myenteric plexus, which release NO and cause relaxation of the LES.
- Within <2 seconds of a swallow, the LES relaxes and remains relaxed for 5 to 7 seconds, until the esophageal pressure wave from the migrating contraction pressure wave of the primary peristaltic wave reaches the distal esophagus.
- Physiological reflux of gastric contents may occur during these times of transient lower esophageal pressure (TLES) relaxation.
- Tertiary peristalsis results from an intramural mechanism which is unrelated to the swallowing centre.
- Tertiary peristalsis is a pathological process, which may include diffuse esophageal spasm resulting in dysphagia for liquids, as well as NCCP (non-cardiac chest pain).
- In a clinical setting, the acidity and the motility of the esophagus can be measured, and demonstrate the pattern of the esophageal body and the pressure of the UES and LES.
- There are variety of modulators of LES pressure

- Modulation of Reflux

Modulators	↑ LES Pressure	↓ LES Pressure
➤ GI hormones/peptides	○ Gastrin ○ Motilin ○ Substance P	– Secretin – Cholecystokinin – Somatostatin – VIP
➤ Neural agents	○ α-Adrenergic agonist ○ β-Adrenergic antagonists ○ Cholinergic agonists	– α-Adrenergic antagonists – β-Adrenergic agonist – Cholinergic antagonists
➤ Foods	○ Protein	– Fat – Chocolate – Peppermint

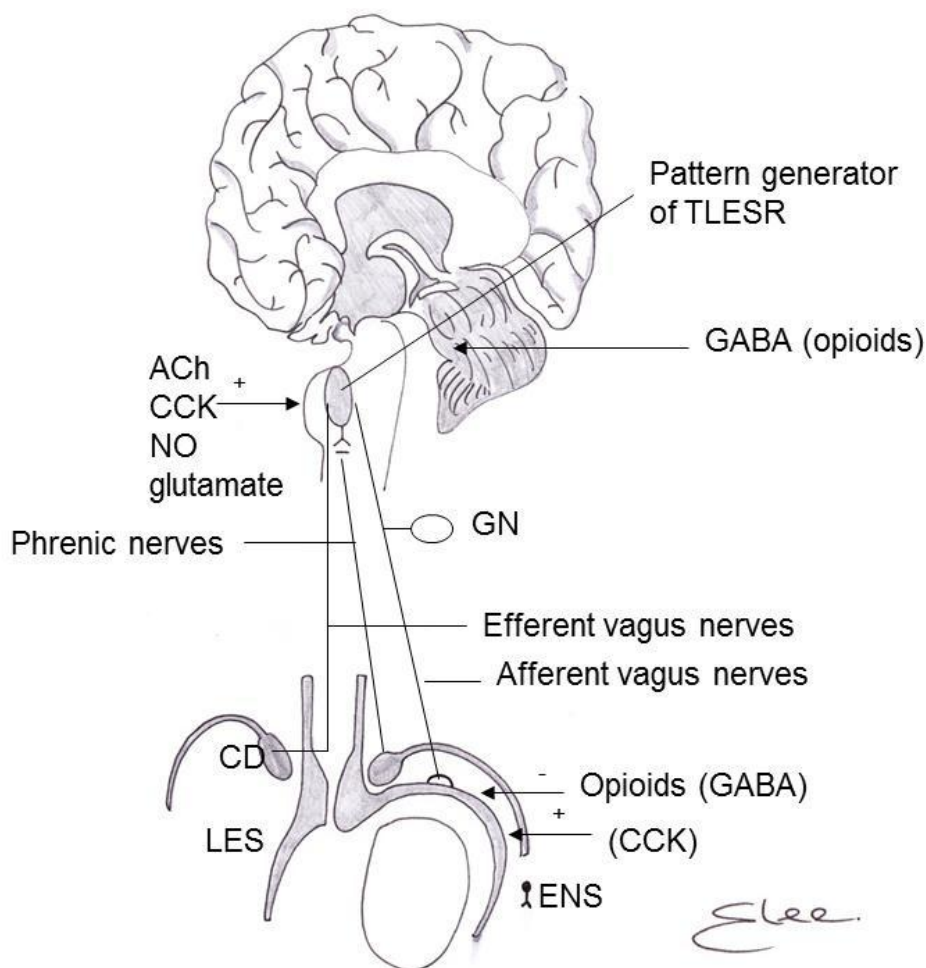
Modulators	↑ LES Pressure
➤ Other factors	○ Histamine ○ Antacids ○ Metoclopramide ○ Domperidone ○ Cisapride ○ Prostaglandin F_{2α} ○ Baclofen

Abbreviations: LES, lower esophageal sphincter; VIP, vasoactive intestinal peptide

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 43-1, page 708, Ninth Edition, 2010

➤ Transient LES relaxation (TLESR)

Transient Lower Esophageal Sphincter Relaxations (TLESRS) and Inhibition of the Crural Diaphragm (Cd) Relax The LES



Abbreviations: Ach, acetylcholine; CCK, cholecystokinin; ENS, enteric nervous system; GABA, gamma aminobutyric acid; GN, nodose ganglion; LES, lower esophageal sphincter; NO, nitric oxide

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 41-1, page 668, Ninth Edition, 2010

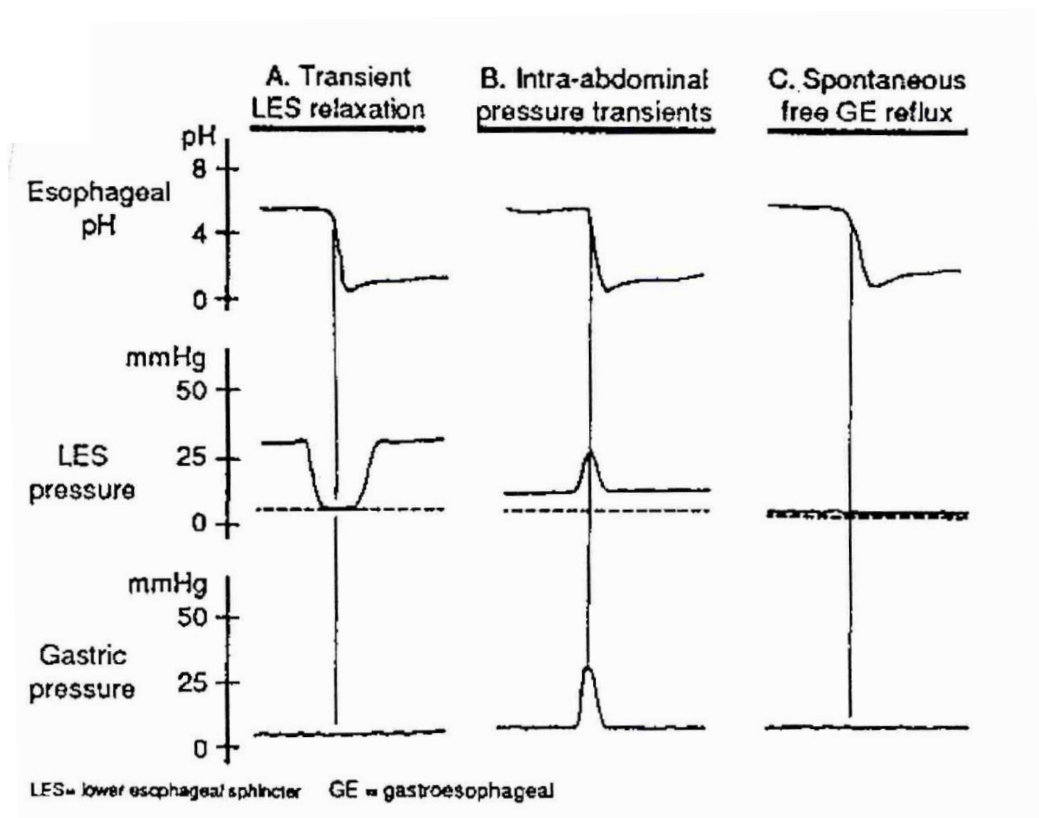
- Some spontaneous and transient relaxation of the LES may occur independently of a swallow, relaxation of the LES, some EE reflux, and thus possibly related to distension of the gastric fundus, and again mediated through release of the neuroinhibitor, NO.
- Peripheral and central pathways mediating transient lower esophageal sphincter relaxations (TLESRs) and associated inhibition of the crural diaphragm (CD)
- The TLESR leads to some small “physiological” amounts of exposure of the lower portion of the esophageal mucosa to gastric hydrochloric acid (HCl).
- Afferent activity from the esophageal submucosa transmits cognitive sensation from the frontal lobe affecting the swallowing process.
- TLESR occurs when distention of the gastric fundus inhibits the GABA pathway.
- TLES may be more important than LES pressure in the pathogenesis of gastroesophageal reflux disease.
- Glutamate or GABA (γ -aminobutyric acid) are neurotransmitters.
- Glutamate/GABA inhibit neurons in the NTS (nucleus tractus solitarius)
- Neurons in NTS synapse with neurons in DMN (dorsal motor nucleus) of vagus nerve
- Neurons in vagus from DMN project to LES (causing lower esophageal sphincter relaxations)
- To reduce TLESRs, block the vagal stimulation (DMN – NTS)
- Giving baclofen, a GABA type B agonist, inhibits DMN, NTS, vagal inhibition of LES, and reduces TLESRs
- AEs (adverse effects) of baclofen include dizziness, weakness, nausea, confusion (about 10% incidence of each)

Adapted from: Vakil et al., *Am. J. Gastro.* 2011; 106: 1427-1438

Gastroesophageal Reflux Disease

- The commonest disorder of the esophagus is GERD (gastroesophageal reflux disease)
- GERD is caused by regurgitation of gastric acid into the esophagus for intervals which are longer than normal ("physiological")
- The mechanism of GERD include excessive TLESR (transient lower esophageal sphincter relaxation, intraabdominal transients, and spontaneous GE reflux. In many GERD patients, the baseline LES pressure is reduced.

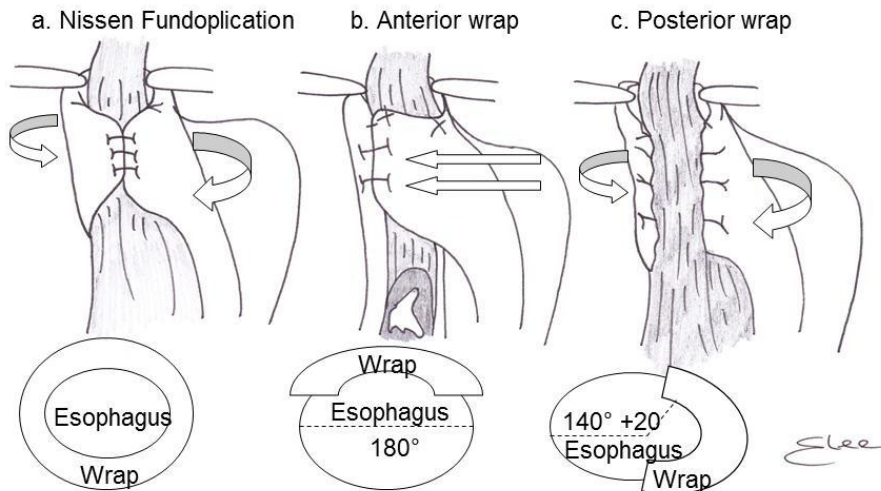
MECHANISMS OF GERD



Abbreviations: LES, lower esophageal sphincter; GE, gastroesophageal

In some GERD patients, when life-style changes (such as weight loss in the setting of increased BMI [obesity]) and medical therapeutics fail, the surgical enhancement of LES pressure and surgical correction of an associated hiatus hernia may be considered.

SURGICAL TREATMENTS FOR GERD



Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Figure 43-15, page 723, Ninth Edition, 2010.

Swallowing

CLINICAL PHYSIOLOGICAL CHALLENGE - Dysphagia

Case: A 45 year old woman develops painless difficulty with swallowing liquids. She has no ENT symptoms, and a barium swallow and EGD (esophagogastroduodenoscopy) are normal. She is suspected as having an esophageal motility disorder.

Questions: Give the physiology of swallowing and describe the features of an esophageal motility tracing which characterize three motility disorders of the esophagus.

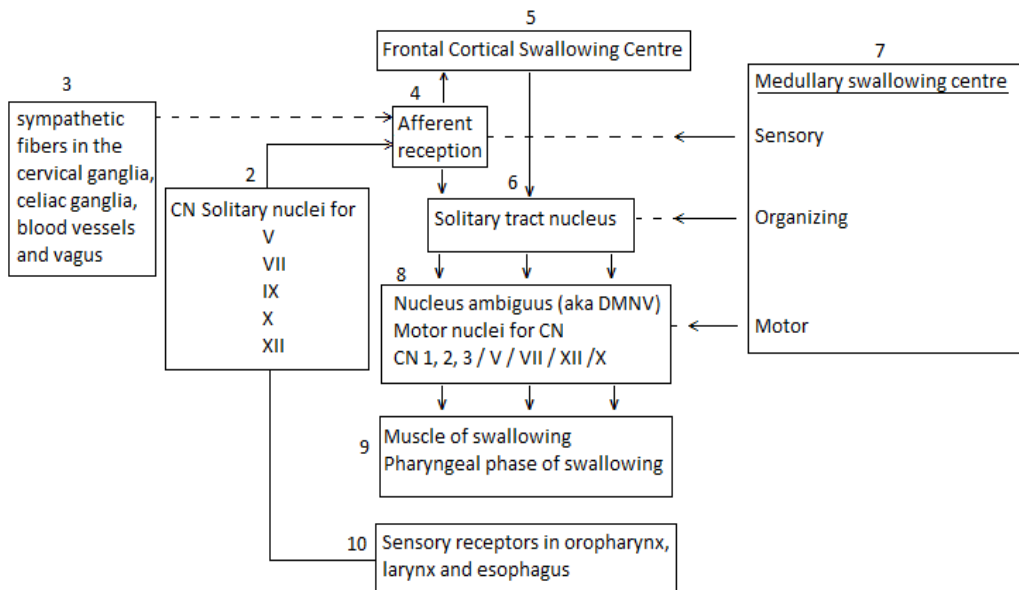
- Important Anatomy
 - Primary motor cortex, with extension into inferior frontal region – mylohyoid portion of swallowing
 - Anterior and medial areas of premotor complex – pharyngeal portion of swallowing

- Medulla: brainstem swallowing centres
- Pons: sensory nucleus, and solitary nucleus

Abbreviations: STN, solitary tract nucleus; SN, sensory nucleus; NA, nucleus ambiguus; DMNV, dorsal motor nucleus of the vagus; CN, cervical nerves

- After ingestion and mastication of food, saliva is secreted, and a food bolus is swallowed.
- 1) Voluntary initiation of swallowing begins in the frontal cortex (cortical swallowing centre)
- 2) Sensory receptors in the oropharynx, larynx and esophagus act through afferent pathways to the sensory nuclei of cranial nerves (CN) V, VII, IX and XII (2).
- 3) Sensation also goes by way of sympathetic fibers in the cervical ganglia, celiac ganglia in the vascular supply as well as through the vagus nerve, reaching the spinal cord segments C1-C3.
- Afferent activity transmits cognitive sensation to the frontal lobe.
- 4) afferent reception passes to
- 5) frontal cortical swallowing centre, and to
- 6) Brainstem medullary swallowing centre (medulla, pons sensory nucleus, solitary tract nucleus).
- 7) The medullary swallowing centre organizes the sensory and motor activity.
- Efferent activity is to the nucleus ambiguus.
- 8) The nucleus ambiguous (aka dorsal motor nucleus of the vagus [DMNV]) acts as a central pattern generator to coordinate activation of the motor nuclei CNS V, VII, X, XI; and C1, C2, C3, and the skeletal muscles of the upper portion of the esophagus, including the pharyngeal component of swallowing.
- The smooth muscle of the lower portion of the esophagus is also coordinated through the DMNV.
- 9) The tongue voluntarily moves the food bolus into the pharynx, in preparation for the pharyngeal phase of swallowing.

CENTRAL CONTROL OF SWALLOWING



CLINICAL PHYSIOLOGICAL CHALLENGE – Pathophysiology of GERD

Case: A 45 year old man with an increased BMI of 29 began to develop severe retrosternal burning discomfort and acid regurgitation when his new –onset hypertension was treated with a calcium channel blocker. His symptoms of gastroesophageal reflux disease (GERD) were worsened by bending forward after meals, and by eating chocolate.

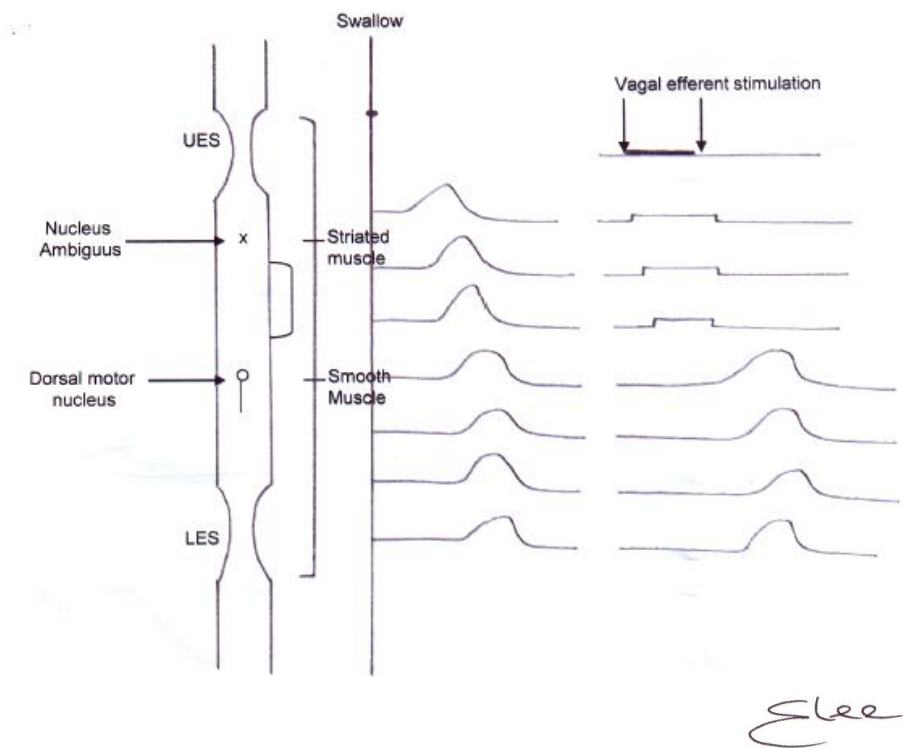
Questions: What is the pathophysiology of GERD?

→ In giving your answer, please include the manometric pressure valves of the upper (UES) and lower esophageal sphincter (LES), as well as the characteristics of the peristaltic waves of the esophageal body

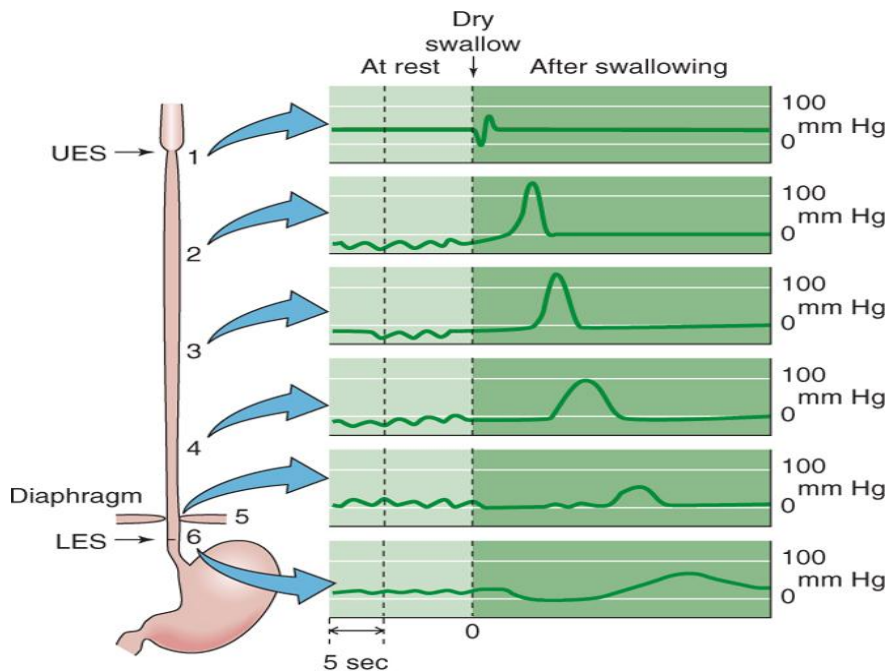
- Structure and function of esophagus
- Tone and relaxation of LES
- Peripheral and central pathways mediating transient lower esophageal sphincter relaxations
- Conditions associated with GERD
- Maintenance of integrity of esophageal mucosal membrane

- The action of cholinergic (Ach) activity on M3 receptors stimulates the esophageal body circular and longitudinal smooth muscle, whereas NO has an inhibitory effect on this smooth muscle.
- Swallowing evokes sequential esophageal contractions that pass smoothly from the striated-to the smooth muscle segments of the upper one-third and lower two-thirds of the esophageal body, respectively.

ESOPHAGEAL PERISTALTIC CONTRACTIONS EVOKED BY SWALLOWING



ESOPHAGEAL TRANSIT OF FOOD



- 1) The striated muscle in the upper third of the esophagus is innervated by the vagal efferent fibers in the recurrent laryngeal nerve.
- 2) In the striated muscle esophagus, vagal stimulation causes simultaneous contractions that occur only during the period of stimulation.
- 3) Thus, the striated muscle esophagus is dependent on central neuronal sequencing for its peristaltic contraction.
- 4) Stimulation of the vagus nerve, evokes peristaltic contractions only in the smooth muscle segment of the esophagus.
- 5) Intrinsic neuronal mechanisms are capable of producing a peristaltic sequence in the smooth muscle segment.
- 6) After a dry swallow, the pressure wave of primary peristalsis moves sequentially down the esophagus.
- 7) Hyperpolarization and no inhibition of the smooth muscle proceeds the cholinergically mediated smooth muscle contraction.

- 8) The distally increasing duration of the latency gradient caused by NO inhibition/hyperpolarization of the smooth muscle, followed by cholinergic contraction and a distally moving contraction pressure wave, leads to progressive movement of the bolus along the length of the esophagus by way of this primary peristalsis.
- 9) The LES pressure falls in anticipation of a bolus of food/fluids passing along the length of the esophagus, through the area of now relaxed LES, and into the stomach.
- 10) Sensory receptors in the body of the esophagus may be stimulated by distention, and result in secondary peristalsis; this secondary peristalsis helps to return to the stomach the small amounts of food/fluid which may be normally regurgitated into the esophagus from the stomach.

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 41-4, page 891.

- 11) The normal tracing (“esophageal transit of food”) shows sequential “peristaltic” contractions in the esophageal body, with full LES relaxation occurring with a swallow.
- 12) The lower tracing shows the peristaltic contractions of the esophageal body resulting in the movement of a food bolus from the upper to the lower end of the esophagus in about 10 seconds.
- 13) Given the complexity of the swallowing process, and the integration of factors necessary to prevent gastroesophageal reflux, it is not surprising that there are a number of esophageal motility disorders.

Esophageal Motility Disorders

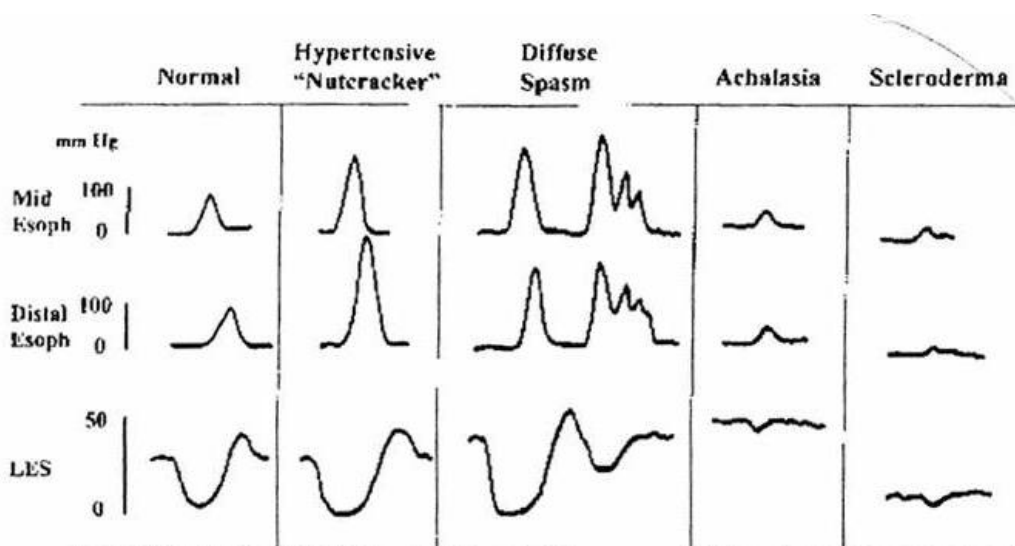
Disorder	Chicago Classification Criteria
➤ Normal EGJ Relaxation (Mean Integrated Relaxation Pressure < 15 mm Hg)	
○ Aperistalsis	– 100 % of swallows with absent peristalsis
○ Hypotensive peristalsis	– More than 30% of swallows with peristaltic defects ≥ 3 cm in 30 mm Hg pressure isocontour
○ Intermittent	– 70% or more of swallows with peristaltic defects ≥ 3 cm in 30 mm Hg pressure isocontour
○ Frequent	– Normal CFV, mean DCI > 5000 and < 8000 mm Hg.s.cm or LES after-contraction > 180 mm Hg
○ Hypertensive peristalsis	– Normal CFV, mean > 8000 mm Hg.s.cm
○ Spastic nutcracker	
○ Diffuse esophageal spasm (DES)	– Normal EGJ relaxation and spasm (CFV > 8 cm/s) with $\geq 20\%$ of swallows
➤ Impaired EGJ relaxation*	
○ Classic Achalasia	– Impaired EGF relaxation and aperistalsis
○ Achalasia with esophageal compression	– Impaired EGF relaxation, aperistalsis, and panesophageal pressurization with $\geq 20\%$ of swallows
○ Spastic Achalasia	– Impaired EGF relaxation, a peristalsis and spasm (CFV > 8 cm/s) with $\geq 20\%$ of swallows (see Fig 42-13C and D)
○ Functional EGF obstruction	– IBP > 30 mm Hg compartmentalization between the peristaltic wavefront (normal or nutcracker) and EGF

*mean integrated relaxation pressure ≥ 15 mm Hg

Abbreviations: CFV, contractile front velocity; DCI, distal contractile integral; EGF, esophagogastric junction; EGJ, esophagogastric junction; IBP, intrabolus pressure; LES, lower esophageal sphincter.

Printed with permission: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 42-2, page 699, Ninth Edition, 2010

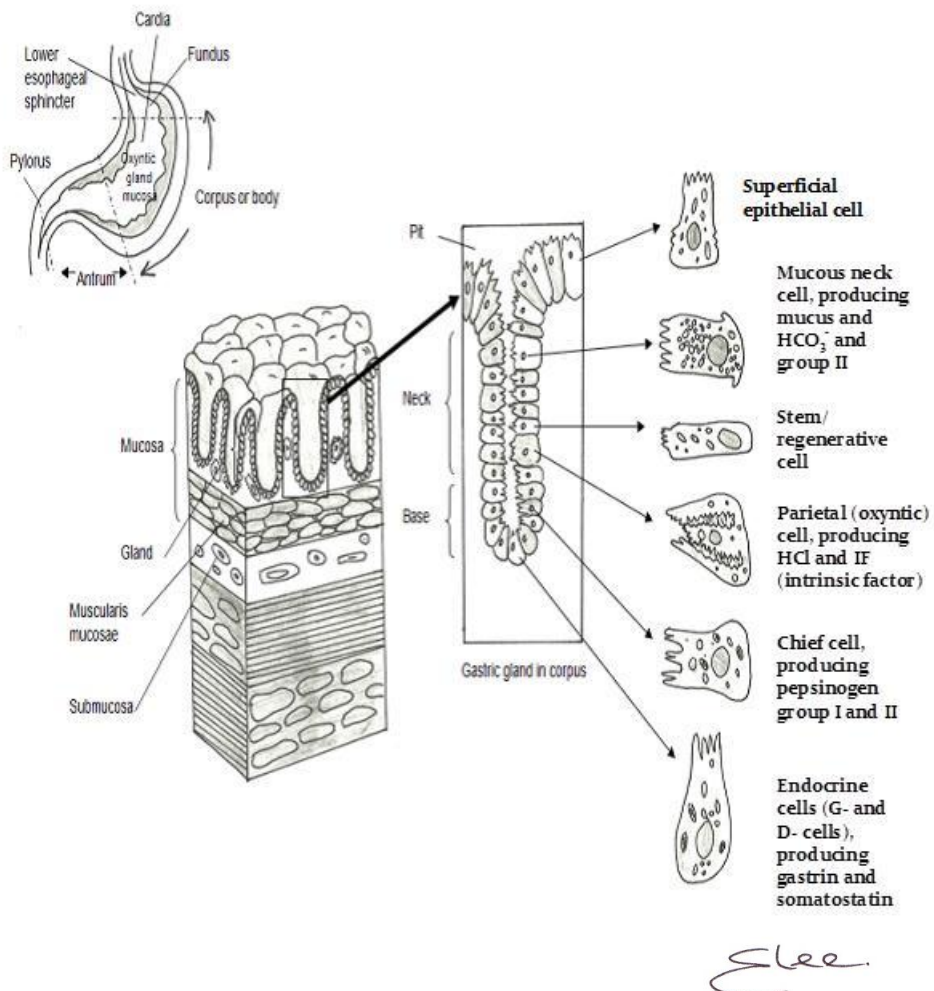
MANOMETRIC FEATURES OF THE MAJOR ESOPHAGEAL MOTILITY DISORDERS



- In diffuse esophageal spasm, normal peristaltic waves are interspersed with high-pressure, nonpropulsive (simultaneous) contraction waves that are often repetitive.
- In achalasia, the resting LES pressure may be abnormally high, contractions of the esophageal body are simultaneous and propulsive, resting intraesophageal pressure is elevated, and swallow-induced LES relaxation is either absent or incomplete.
- Scleroderma is characterized by the presence of weak, nonperistaltic esophageal contractions, and a marked hypotensive LES that relaxes normally with swallowing.

STOMACH

Gastric Anatomy



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 42-1, page 896.

Give the cells of the stomach and their function

Cells	Function
➤ Parietal (oxyntic) Cell	
○ Hydrochloric acid	– Provides optimal pH for pepsin and gastric lipase (see below) – Assists duodenal inorganic iron absorption (reduction of food Fe^{3+} to Fe^{2+}) – Negative feedback of gastrin release (when intragastric acidity falls, serum gastrin concentration rises) – Stimulation of pancreatic HCO_3^- secretion – Suppression of growth of microorganisms ingested in food
○ Intrinsic factor	– Binding of vitamin B_{12} for subsequent ileal absorption
➤ Chief (Peptic) Cell	
○ Pepsins	– Initial hydrolysis of dietary proteins – Liberation of vitamin B_{12} and Fe^{3+} from dietary protein
➤ Superficial epithelial cell	– Maintains barrier function of gastric membrane
➤ Endocrine Cell	
○ Gastrin secreting somatostatin G- cells	– Stimulate acid secretion
○ Somatostatin secreting D-cells	– Inhibit acid secretion

Cells	Function
➤ Mucous Neck Cell	
○ Mucin/HCO ₃ ⁻	- Protection against noxious agents including hydrochloric acid and pepsins

*In addition to assisting digestion and absorption of dietary protein, hydrolysis of certain dietary proteins may render them harmless in individuals who may be allergic to these proteins (i.e., pepsin may prevent certain food allergies).

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q. the surface of the stomach and intestine possess many defensive mechanisms, including trefoil factors.

- Give the physiological effect of trefoil factors.
- A.
 - Source
 - pS2 gastric mucus neck cells
 - spasmolysin gastric antrum and pancreas
 - intestinal trefoil factor goblet cells in small intestine and colon
 - Composition
 - Cloverleaf shape
 - 6 cysteine residues and 3 disulfide bonds
 - Action
 - Secreted mucus – mucosal surface
 - Growth – promoting properties

Gastric Hydrochloric Acid Secretion at the Macromolecular level

CLINICAL PHYSIOLOGICAL CHALLENGE – Hypergastrinemia and Acid Hypersecretion

Case: A 35 year old man with dyspepsia and diarrhea was found on upper GI endoscopy to have three ulcers in the second portion of the duodenum. He did not take ASA or NSAIDs, and his antral biopsies taken before acid lowering therapy were negative for *H. pylori*. A fasting serum gastrin concentration was 750 pg/ml. You suspect that he may have a gastric hypersecretion state.

Question:

- Give the physiology of gastric secretion of hydrochloric acid and pepsinogen, the mechanisms of the control of acid secretion, and the pathophysiology of the hypergastrinemia and hyperacidemia seen in persons with gastrinoma
- Explain the scientific basis for the calcium – infusion and the secretin tests for Zollinger-Ellison Syndrome, and the rate of measuring BAO and MAO.
- Outline the mechanisms of diarrhea in this patient

Abbreviations: BAO, basal acid output; MAO, maximal acid output

➤ Gastric membrane permeability at the macro' level

- The gastric epithelium acts as a very strong permeability or diffusion barrier for H^+ and Na^+ :
- This tight defensive barrier is created by the tight junctions (TJs) between the gastric epithelial cells, the hydrophobicity of the lipid membrane of the cells, secreted mucous and HCO_3^- , the alkaline microclimate adjacent to the gastric cellular membrane, prostaglandins, and the maintenance of normal blood flow and capillary function.
- Mucus is a viscous gel, which contains water, electrolytes, and phospholipids as well as glycoproteins.
- Mucus produced and released from glands in the gastric antrum, is a neutral glycoprotein.

- Mucus from the surface and neck cells contains both neutral as well as acidic glycoproteins.
- Mucus is secreted as the result of Ach release from the vagus nerve which becomes stimulated from gastric mucosal irritation by the direct contact of food on the gastric mucosa, or the indirect effect of chemicals such as pickles and red peppers.

Acid Secretion

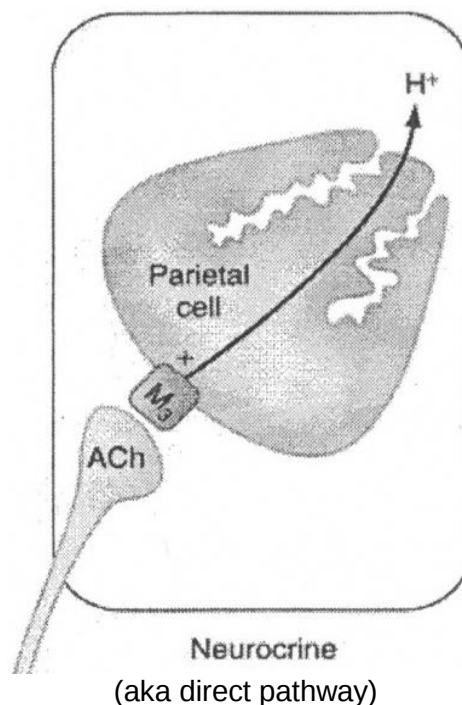
Main Diseases:

- Peptic ulcer disease
- Helicobacter pylori infection
- Acid hypersecretion disorders
- Gastroparesis

Gastric function:

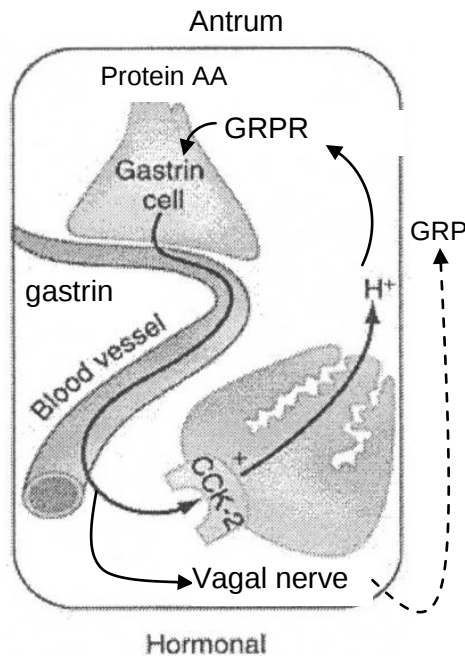
- Reservoir for food
- Synthesizing and secreting HCl and pepsinogen as well as mucus and intrinsic factor
- Mixing of food with HCl and pepsinogen
- Control the release of partially digested food into the duodenum
- Assist in the control of appetite and food intake.
- Gastric alcohol dehydrogenase may metabolize small amounts of ingested alcohol.
- Basal (interdigestive) gastric acid secretion
 - Basal; basal acid output (BAO) ie (secretion), ~5mEq/L of gastric juice
 - BAO – low in morning, higher in later day

- BAO increases with the number of parietal cells, which increases in proportion to a person's body weight
 - When gastric secretion is constantly stimulated, such as in patients with the Zollinger-Ellison Syndrome (ZES), the basal acid secretion is increased more than the stimulated secretion
- Stimulated gastric HCl secretion
- There are the overlapping cephalic (CNS), gastric and intestinal phases, which enhance acid secretion.
 - Acetylcholine (ACh; neuronal stimulation), gastrin (hormonal) and histamine (paracrine) are the gastric stimulants. Each of these have receptors (M3, CCK_B and histamine – 2 receptors, respectively) on both the parietal cell (direct pathway) H and the ECL (enterochromafin cell, indirect pathway).



Abbreviation: ACh, acetylcholine; M3, muscarinic receptor

- Neuroendocrine (cephalic; release of acetylcholine [ACh] and its action on the M3 receptor of the parietal cell



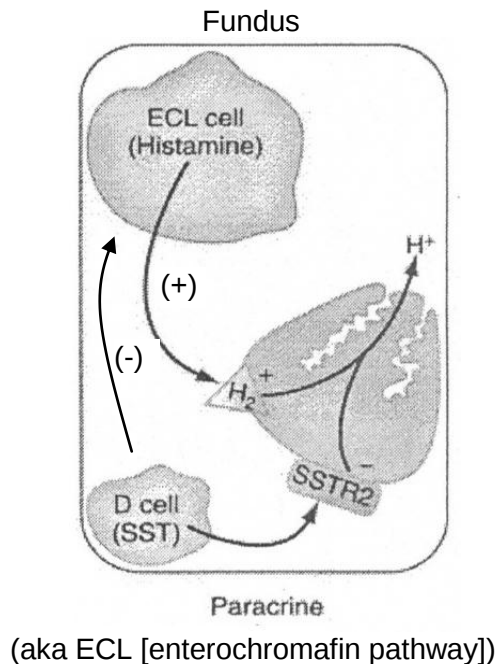
Abbreviations: CCK, cholecystokinin; GRP, gastrin releasing peptide; GRP-P, gastrin releasing peptide receptor

- The hormonal pathway (release of gastrin from the G-cell, and its action on the CCK-2 receptor of the parietal cell, as well as the release of the gastrin – releasing peptide (GRP) from the vagus nerve, and the action of GRP on the G-cell.
- The paracrine pathway

CLINICAL PHYSIOLOGICAL CHALLENGE – Physiology of Gastric Acid Secretion

Background: Gastric parietal cells secrete hydrochloric acid (HCl). The apical (luminal) membrane contains H^+/K^+ ATPase, as well as a Cl^- and a K^+ channel. The basolateral membrane contains Na^+/K^+ ATPase, a Na^+/H^+ exchanger (NHE), as well as a K^+ and a HCO_3^-/Cl^- channel.

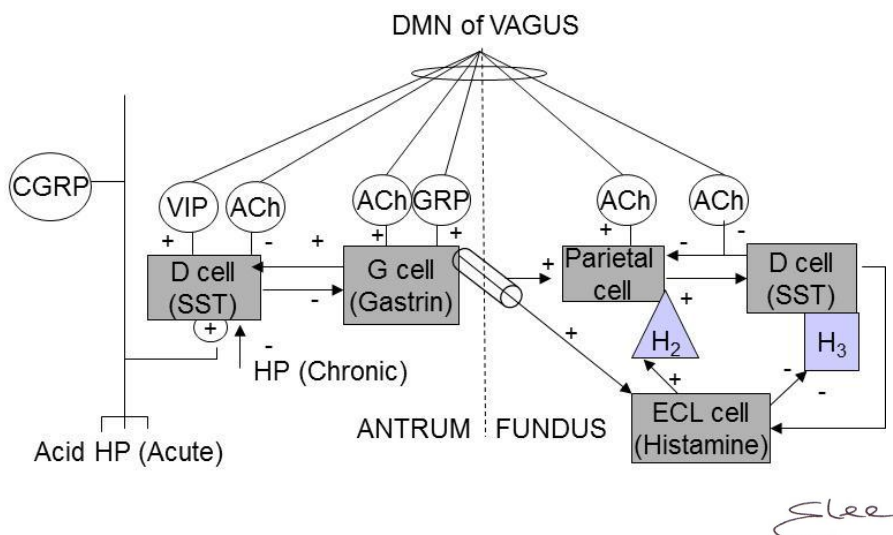
Problem: With these membrane components, draw a diagram which depicts the steps in the gastric parietal cell secretion of HCl and fluid.



- Release of histamine from the ECL cell.
- Binding of histamine to the H_2 receptor of the parietal cell.
- Stimulation of acid secretion.
- Release of somatostatin [SST] from the D cell.
- SST binds to the $SSTR_2$ on the parietal cell, reducing acid secretion.
- SST reduces histamine release from ECL cell.
 - Neuroendocrine, hormonal, and paracrine pathways directly regulate parietal cell acid (H^+) secretion.

Abbreviations: Ach, acetylcholine; GRP-R, gastrin-releasing peptide receptor, and SST also have important indirect actions affecting acid secretion not shown here. +, stimulatory; -, inhibitory.

Adapted from: *Sliesenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 49-1, page 818, Ninth Edition, 2010



Abbreviations: Ach, acetylcholine; CGRP, calcitonin gene related peptide; ECL, enterochromafin-like cell; DMN, dorsal motor nucleus; GP, gastrin releasing peptide; Hp, H. pylori; SST, somatostatin

• Cephalic and Gastric Phases of Acid Secretion

Name Gastrointestinal Peptide Hormones, their source and their action on the stomach

Hormone	Source	Action
○ Gastrin (G)	G cells, antrum of stomach	↑ H^+ secretion
○ Gastrin-releasing peptide (GRP)	Vagal nerve endings	↑ Gastrin release
○ Acetylcholine	Vagal nerve endings	↑ HCL secretion
○ Histamine	ECL cells; Releases GRP from PPP and ENS neurons	↑ G from G cells, ↓ SST from D cells
○ Secretin	S cells in small intestine	↑ HCO_3^- and fluid secretion by pancreatic ducts
○ Somatostatin	D cells of stomach and duodenum, islet cells of pancreatic islets	↓ Gastrin release

Hormone	Source	Action
○ Motilin	Endocrine cells in upper GI tract	↑ Smooth muscle contraction
○ Peptide YY (PYY)	Endocrine cells in ileum and colon	↓ Vagally mediated acid secretion

Printed with permission: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Table 41-1, page 889.

CLINICAL PHYSIOLOGICAL CHALLENGE – Turning Acid Secretion On and Off

Background: The stomach has a series of integrated control systems to mediate the secretion of HCl and pepsin to initiate the process of digestion of food. But an excess of HCl and pepsin can damage the mucosa of the stomach and duodenum, causing ulceration with its associated problems of hemorrhage, obstruction and perforation.

Problem: Describe in detail how the stomach turns on and then turns off hydrochloric (HCl) acid secretion

- There are numerous peptide-hormones produced by the GI tract, and many of these are involved in the regulation of gastric hydrochloric acid secretion.

➤ Acetylcholine

- 1) The cephalic phase is responsible for about 30% of total stimulated acid secretion
- 2) The site, smell, and taste of food activate the dorsal motor nucleus (DMN) of the vagus nerve in the medulla.
- 3) The parasympathetic preganglionic nerves release acetylcholine (ACh), which in turn stimulates acid secretion (parietal cells and ECL cells, [GRP, G cells and D cells]).
- 4) The stimulated vagus nerve releases acetylcholine (ACh) and gastrin-releasing peptide (GRP).
- 5) Acetylcholine (ACh) released from postganglionic intramural neurons within the oxyntic mucosa stimulates the parietal cell directly

via M3 receptors, coupled to the release of intracellular calcium (Ca^{2+}).

- 6) Efferent vagal fibers synapse with intramural gastric cholinergic (ACh) and peptidergic (gastrin releasing peptide [GRP] and vasoactive intestinal peptide [VIP]) neurons.
- 7) In the fundus (oxyntic mucosa), ACh neurons stimulate acid secretion, thus eliminating its restraint on parietal cells and histamine containing enterochromaffin like (ECL) cells. In the antrum (pyloric mucosa), ACh neurons stimulate gastrin secretion directly as well as indirectly by inhibiting SST secretion, thus eliminating its restraint on gastrin containing G-cells.
- 8) ACh directly acts on the M3 receptor on the basal membrane (BM) of the parietal cell, as well as ACh binds to the enterochromaffin-like ECL cell.
- The binding of the ACh to the M3 receptors on the parietal cell and to the ECL cell stimulates the parietal cell directly as well as indirectly (respectively)

➤ Somatostatin

- Release of acid into the lumen of stomach restores SST secretion in both the fundus and the antrum is mediated via the release of calcitonin gene related peptide (CGRP) from extrinsic sensory neurons.
- Acid in the lumen of the gastric antrum releases somatostatin (SST)
 - SST inhibits antral G-cell gastrin release, and thereby inhibits HCL secretion (protein $\rightarrow \uparrow \text{G}$, $\uparrow \text{ACh}$ - $\uparrow \text{HCl}$ - $\uparrow \text{SST}$ - $\downarrow \text{G}$ $\rightarrow \downarrow \text{HCl}$)
- ACh inhibits the release of somatostatin (SST) from the D cells of the stomach and duodenum, thereby increasing acid secretion by reducing this inhibitory influence of SST.
- The gastric phase is responsible for about 60-65% of total stimulated acid secretion.
- Distention of the gastric wall by food activates indirectly stimulates acid secretion by activating the vagal afferent and efferent pathway (vagovagal) and ENS reflexes.

- Alcohol, coffee, and peptones (partially digested protein) in the gastric lumen also stimulate the release of antral G cell gastrin.
- Somatostatin (SST)
 - SST from D cell represents a redundant regulatory pathway, which inhibits acid secretion.
 - SST binds $SSTR_2$ on basal membrane of parietal cell, reducing acid secretion.
 - SST acts directly on ECL cells to reduce histamine release, and to thereby further decrease acid secretion.
- SST reduces
 - antral gastrin release from antral G cells
 - inhibits histamine release from ECL cells
 - SST-28 is more abundant than SST-14. SST secretion by the D cells.
- Histamine released from ECL cells act via H_2 receptors on D cells to inhibit SST secretion.
- Acute infection with *Helicobacter pylori* (Hp) also activates CGRP neurons to stimulate SST and thus to inhibit gastrin secretion.
- In duodenal ulcer patients who are chronically infected with Hp, the organism or cytokines released from the inflammatory infiltrate inhibit SST, and thus stimulate gastrin (and thereby acid) secretion.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Figure 49-10, page 822, Ninth Edition 2010.

➤ Gastrin

- 1) Products of protein digestion (i.e., peptides and amino acids)
 - Stimulate the G cells to release gastrin
 - Stimulate GRP (gastrin-releasing peptide) release from the vagal nerve endings
- Gastrin, released from antral G cells, travels in the systemic blood circulation to reach the parietal cell.

- 2) The gastrin binds to the CCK_2 receptor directly activates cholecystokinin-2 (CCK-2) receptors on the parietal cells and leads to the release of intracellular calcium.
- This stimulates the post-translational modification of G-101 (the 101 amino acid containing gastrin) in the trans-Golgi apparatus of the endoplasmic reticulum (ER) of the G cells.
- 3) GRP releases gastrin from antral G cells, and reduces the release of somatostatin (SST) from gastric body and antral D-cells.
- The release of gastrin from the G-cells is mediated from the luminal and anti-luminal sides of the G-cell.
- This post-translational modification of G-101 results in G-17 and G-34.
- 4) G-17 and G-34 are present as gastrin I (non-sulfated) and gastrin II (sulfated).
- 5) In the plasma, G-17 is inherently more active, but is degraded faster than the less active but more slowly degraded G-34.
- Because of the differences in their inherent activity and rates of degradation in the plasma, G-17 and G-34 have similar potency, mole per mole.
- The parietal cell H^+ secretion is stimulated by way of CCK_B , Cq, PLC, IP3, and DAG.
- The M_3 and CCK_B receptors couple to a GTP-binding protein. The Gqi receptor activates PLC (phospholipase C).
- Gastrin-releasing peptide (GRP)
 - GRP from PPP/ENS neurons as well as Ach stimulate the antral G cells to release gastrin.
 - GRP neurons, activated by luminal protein, also stimulate gastrin secretion. VIP neurons, activated by low grade gastric distention, stimulate SST and thus inhibit gastrin secretion.

➤ Histamine

- 1) Ach and gastrin binding to the M3 and CCK_B receptors on the outer membrane of the ECL release histamine from the ECL cells
- Histamine released from oxyntic ECL cells diffuse to the parietal cells (paracrine effect), and stimulates the release of GRP from
 - peptidergic postganglionic parasympathetic (PPP) neurons
 - as well as ENS neurons.
- 2) Histamine released from ECL and from mast cells from
 - binds to the histamine H₂ receptor on the basal membrane (BM) of the parietal cell.
- 3) Histamine coupled to GIs
 - couples to G1s (another GTP-binding protein)
 - activates AC (adenyl cyclase) to form cAMP
- cAMP activates PKA (protein kinase A).

➤ Calcium

- 1) Phospholipase C (PLC) cleaves PIP2 (phosphatidyl inositol 4, 5-b1 phosphate) in the BM of the parietal cell to IP3 (inositol 1,4,5-triphosphate) and DAG (diacylglycerol).
- 2) IP3 releases Ca²⁺ stored in the ER (endoplasmic reticulum) of the cytosol of the parietal cell.
- M3 activates a Ca²⁺- channel in the BM of the parietal cell, leading to a further increase in intracellular Ca²⁺ [Ca²⁺]_i
- 3) [Ca²⁺]_i is also increased from the Ca²⁺-channels activating calmodulin-dependant protein kinase.

• **The Intestinal Phase**

➤ Stimulation of Gastric and Acid Secretion

- Protein digestion products (partially digested peptides and amino acids) stimulate duodenal G cells to secrete gastrin, which stimulates the parietal cell.

- Protein digestion products act on an unknown intestinal endocrine cell to release an unknown hormone (named entero-oxyntin), which stimulates the gastric parietal cell to produce hydrochloric (HCl) acid.

➤ Inhibition of Gastric Acid Secretion

- In addition to the intestinal phase which stimulates gastric acid secretion, there is an intestinal phase which inhibits acid secretion.
- Loss of Gastric Stimulation
 - Loss of the stimulatory Ach, gastrin and histamine, as well as the emptying of the stomach and loss of gastric stimulatory signals, causes “inhibition” of parietal cell acid secretion.
- Gastric Inhibitory Peptide (GIP)
 - GIP is released from K cells in the duodenum and jejunum as the result of fat and glucose in the lumen.
 - GIP reduces antral gastrin, and directly reduces acid secretion by the parietal cell.
- Secretin
 - Fat as well as acid in the duodenum release secretion from S cells in the small intestine.
 - Gastric acid entering the duodenum initially causes an acidic environment in the lumen.
 - As pH falls below 4.5, secretin is released from the duodenal S cells.
 - Secretin acts as an enterogastrone (inhibitor) in the intestinal phase of gastric acid secretion, inhibiting gastric parietal cell acid secretion.
 - Secretion also stimulates pepsinogen secretion from the gastric chief cells.
- SST arises from D cells in the gastric antrum and fundus, in the duodenum, the islet cells of the pancreas, and by neurons of the hypothalamus
 - SST is increased by luminal acid in the duodenum, but luminal acid has no effect on the G cells in the antrum.
 - SST secretion is decreased by vagal Ach acting on the D cell.

- SST binds to G1 coupled SSTR2 receptors on parietal cells, as well as on ECL cells and G cells tonically restrains acid secretion.
- This restraint is exerted directly on the parietal cell as well as indirectly by inhibiting histamine secretion from ECL cells and gastrin secretion from G-cells.
- SST directly inhibits acid secretion by the parietal cells.
 - The SST receptor and the prostaglandin receptors for prostaglandin E2 (PGE2) couple to a GTP-binding protein on the BM of the parietal cell, (Gq, coupled by M3 receptor and CCK_B receptor, Gs coupled by histamine – two receptors, all in the cytosol of the parietal cell).
 - G1 inhibits the activity of Gs, and thereby reduces cAMP, PKA, and H⁺-pumping by the canalicular membrane proton pump H⁺, K⁺-ATPase.
 - PGE2 binds to EP3 (prostaglandin receptor) on BM of parietal cell, PGE2-EP3 couple to G1.
- Prostaglandin E2 (PGE2)
 - PGE2 reduces histamine release from ECL cells, and inhibits gastrin release from antral G cells.
- Enterogastrones
 - In addition to SST GIP, secretin and PGE2 other enteric hormones inhibit gastric acid secretion (enterogastrones): CCK, VIP, gastric inhibiting peptide (GIP; also better known as “glucose-dependent insulinotropic polypeptide”), neurotensin (NT), and peptide YY (PYY).

CLINICAL PHYSIOLOGICAL CHALLENGE – Parietal cell

Background: Gastric parietal cells secrete hydrochloric acid (HCl). The apical (luminal) membrane contains H⁺/K⁺ ATPase, as well as a Cl⁻ and a K⁺ channel. The basolateral membrane contains Na⁺/K⁺ ATPase, a Na⁺/H⁺ exchanger (NHE), as well as a K⁺ and a HCO₃⁻/Cl⁻ channel.

Problem: With these membrane components, draw a diagram which depicts the steps in the gastric parietal cell secretion of HCl and fluid.

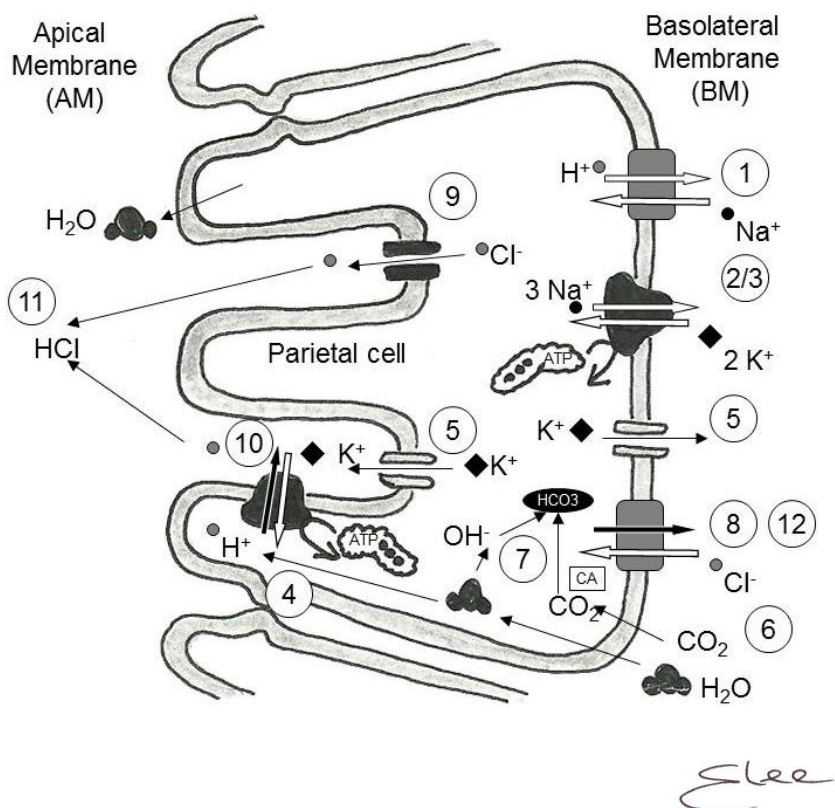
Gastric Hydrochloric Acid Secretion at the Micro' (Cellular) Level of the Parietal Cell

Overview Requirements of the system

- H^+ formed in the cell is secreted across the AM Cl^- is needed to form HCl with the H^+ .
- Cl^- enters the parietal cell from the action of the BM Cl^- / HCO_3^- exchanger.
- Cl^- leaves the cell through the AM Cl^- channel.
- The process is “energized” by the BM Na^+ / K^+ ATPase.

First, the vocabulary of the components

- | | |
|---|--|
| <p>➤ BM</p> <ul style="list-style-type: none"> ○ NHE (Na^+ / H^+ exchanger) ○ ENaCs (epithelial Na^+ channels) ○ CFTR (cystic fibrosis transmembrane receptor) ○ HKE ($H^+ - K^+$ exchanger)(Na^+ / K^+ ATPase – “the pump”) | <p>➤ AM</p> <ul style="list-style-type: none"> ○ CC (Cl^- channel) ○ $NaHCO_3E$ (Na^+ / HCO_3^- exchanger) ○ $Na^+ - K^+$ ATPase ○ KC (K^+ channel) |
|---|--|
-
- 1) Na^+ enters the parietal cell across the BM by way of the Na^+ / H^+ exchanger.
 - Parietal cells in the gastric body have numerous tubulovesicles (TVs) which contain inactive, H^+ , K^+ -ATPase (aka “the acid [or proton] pump”)
 - The beta subunit of the H^+ , K^+ - ATPase is the actual H^+ pump or catalytic unit .



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 42-4, page. 898.

- 2) Na^+ exits across the BM by the Na^+ / K^+ ATPase.
- 3) K^+ enters the parietal cell across the BM by the Na^+ / K^+ ATPase.
- 4) K^+ also enters the parietal cell by the AM H^+ / K^+ ATPase.
- 5) To avoid accumulation of K^+ in the parietal cell, K^+ may exit the parietal cell through the AM or BM K^+ channel.
- 6) CO_2 and water diffuse across the BM.
- 7) Carbonic anhydrase (CA) in the cytosol of the parietal cell forms H^+ plus HCO_3^- (from OH^- plus CO_2).
- 8) Cl^- enters across the BM by the $\text{Cl}^- / \text{HCO}_3^-$ exchanger.

- 9) The Cl^- needed to form HCl in the lumen moves from the cytosol of the parietal cell across a Cl^- channel in the AM.
- 10) The H^+ in the cytosol of the parietal cell is removed by the proton pump on the luminal canalicular membrane.
- With stimulation of the parietal cell (neural, hormonal and paracrine factors), the activated PKA, PCA, Ca^{2+} activate H^+ , K^+ - ATPase.
- The tubulovesicles (TVs) which now contain activated H^+ , K^+ - ATPase are inserted into the canalicular membrane.
- Upon stimulation of the parietal cells, and with the inserting of the TVs with their active proton pumps (H^+ , K^+ - ATPase) into the canalicular membrane, the H^+ is actively secreted into the gastric lumen, in exchange for K^+ in the lumen.
- Together the activated PKA, PKC and Ca^{2+} phosphorylate and activate the previously inactive H^+ , K^+ -ATPase.
- The secretion of gastric hydrochloric acid, HCl, begins.
- 11) In the gastric lumen, the H^+ and Cl^- form HCl.
- When HCl is secreted from the parietal cells in the glands in the gastric body, the acid streams through the overlying mucous and into the gastric lumen.
- The mucous layer reforms, and the mucous layer prevents the subsequent back diffusion of HCl and pepsin.
- 12) The cytosolic HCO_3^- formed from the CA effect on $\text{CO}_2 + \text{H}_2\text{O}$ exits across the BM by the $\text{Cl}^- / \text{HCO}_3^-$ exchanger.
- 13) The surface epithelial cells in the gastric body and antrum secrete HCO_3^- .
- The HCO_3^- is trapped in the mucous / unstirred water layer adjacent to the luminal side of the gastric membrane.
- This trapping of HCO_3^- in the mucous / unstirred water layer forms the alkaline microenvironment close to the AM.

- This alkaline microclimate is protective to the luminal surface of the gastric cells, and thereby forms part of the diffusion or permeability barrier.
- The high concentration of H^+ in the gastric lumen does not readily diffuse through the mucous gel layer, and the microenvironment.
- If any pepsin or acid manages to penetrate into the mucous layer, the pepsin will be rendered inactive because of the alkaline microclimate.
- The back-diffusion of acid from the gastric lumen into cytosol of the parietal cell will also be partially neutralized.

Abbreviations: CCK, cholecystokinin; VIP, vasoactive intestinal peptide; PYY, peptide YY; ENS, enteric nervous system

CLINICAL CHALLENGE – Secretin Test for Gastrinoma

Case: A patient with aggressive peptic ulcer disease complicated by hypercalcemia and diarrhea has fasting hypergastrinemia. A secretin infusion test is undertaken to determine if the patient has biochemical evidence of gastrinoma.

Question: Give the explanation for the increase in the plasma concentration of gastrin following the injection of secretin in the patient with a gastrinoma.

CLINICAL PHYSIOLOGICAL CHALLENGE – MAO/BAO

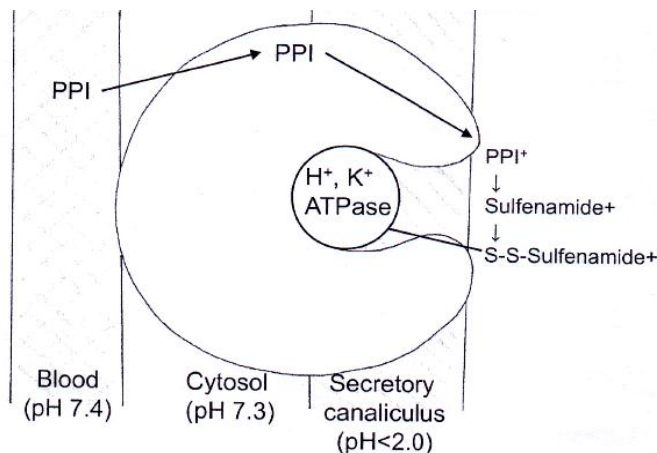
Background:

- The ratio of gastric MAO/BAO (maximal acid output, divided by basal acid output) is much higher than the ratio of maximal to basal pepsinogen secretion.

Question:

- Why? Firstly, the Ach-responsive HCl secretion stimulates a local cholinergic reflex to release even more Ach, and thereby more pepsinogen from the chief cells. Secondly, when HCL empties into the duodenum, secretin is released from duodenal S cells, and secretin also stimulates the chief cells to secrete pepsinogen.

➤ The Mechanism of Action of Proton Pump Inhibitors (PPIs)



See

Adapted from: *Slisenger and Fordtrans's Gastrointestinal and Liver Disease*. Figure 49-15, page 825, Ninth edition, 2010.

CLINICAL PHYSIOLOGICAL CHALLENGE – PK/ PD of PPIs

Case: When an 18 year old man's dyspepsia fails to respond to once a day proton pump inhibitor (PPI), he is reminded to take the medication half an hour before breakfast, and he now enjoys symptom relief.

Question: Give the pharmacokinetics and pharmacodynamics of PPIs and explain why PPIs must be taken half an hour before the intake of food

- The PPIs (proton pump inhibitors) are potent non-competitive inhibitors of the gastric H⁺, K⁺- ATPase
- PPIs are pro-drugs, coated to protect against damage by gastric HCl.
- Acid volume is low in basal state.
- PPIs are taken by mouth by fasting patient, half an hour before breakfast.

- Rapid absorption of PPI in upper small intestine, with C_{max} achieved in about one hour
- PPIs reach parietal cell from the bloodstream, diffuse through the cytoplasm of the unstimulated, fasting, basal state parietal cell and accumulate in the acid environment of the secretory canaliculus.
- Proton pump (H^+ , K^+ ATPase) in the membrane of the canaliculi in the cytosol of the parietal cell are inactive and does not bind PPI or its metabolites.
- With food intake the parietal cells are stimulated.
- In the stimulated state, the canaliculi with inactive H^+ , K^+ -ATPase ("inactive canaliculi") traffics to the apical membrane of the parietal cell.
- In the stimulated, active canaliculus, the PPI becomes protonated, inactive, is trapped as a sulfenic acid, and then is degraded to sulfonamide (PPI-S).
- The canaliculi, in the membrane undergo a change in configuration with activation, exposing their cysteine sites
- The sulfonamide in PPI-S binds covalently by disulfide bonds to one or more cysteines of the H^+ , K^+ -ATPase to inhibit the enzyme.
- All PPIs bind to cysteine 813; omeprazole also binds to cysteine 892, lansoprazole to cysteine 321, and pantoprazole to cysteine 822.
- Binding of PPI-S to canaliculi blocks H^+ , K^+ -ATPase (proton [H^+] pump) and markedly reduces secretion of HCl
- PPI-S block HCl secretion regardless of method of stimulation (Ach, gastrin, histamine)
- Taking PPI half hour before meals provides the time necessary for
 - The PPI to be absorbed, metabolized, and to enter the parietal cell; and for
 - The canaliculi to be stimulated to traffic to and to be inserted into the apical membrane, where the PPI-S can now bind to the H^+ , K^+ ATPase and markedly reduce HCl secretion arising from all forms of stimulation

➤ Response to Secretin Infusion in Health

- Gastrin is synthesized and secreted into the bloodstream by the gastrinoma.
- Gastrin acts via cholecystokinin-2 (CCK-2) receptors on acid secreting parietal and histamine secreting enterochromaffin-like (ECL) cells.
- This increases acid secretion and induces cell proliferation.
- In the antrum, exogenous secretin (given in the secretin stimulation test) stimulates gastrin secretion directly and concomitantly inhibits gastrin secretion by stimulating somatostatin (SST) secretion.
- In health, the balance of the inhibitory and stimulatory effects of secretin on gastrin release is little or no gastrin release.
- ↑ antral release of gastrin
- ↑ gastroduodenal release of SST
- ↑ SST → ↓ gastrin
- Balance of the 2 opposite effects is for secretin to have little effect on serum gastrin concentration.

➤ Response to Secretin Infusion with a Gastrinoma

- Gastrinoma does not contain functionally coupled SST cells, so the usual release of SST is lost, and the stimulatory effect of secretin on gastrin release is unopposed.
- Thus, the effect of secretin in ZES patients is solely to stimulate gastrin secretion from the tumour.
- ↑ antral release of gastrin
- No release of SST, so no ↓ gastrin effect.
- This is the basis for the secretin stimulatory test on gastrin secretion in persons with ZES due to a gastrin-producing tumour (gastrinoma).

CLINICAL PHYSIOLOGICAL CHALLENGE – Peptic Ulcer Therapy

Case: Gastric fluid pH may be reduced by antacids, or by blockage of the histamine-2 (H₂) receptor or the H⁺/K⁺ - ATPase (the proton pump). Peptic ulcer disease develops for several reasons, including the damaging effects of H⁺ and pepsin on the gastric mucosa.

Questions: Apart from the proton pump inhibitors (PPI) producing a lower reduction of gastric acid secretion, what other mechanism likely contributes to their greater healing potential.

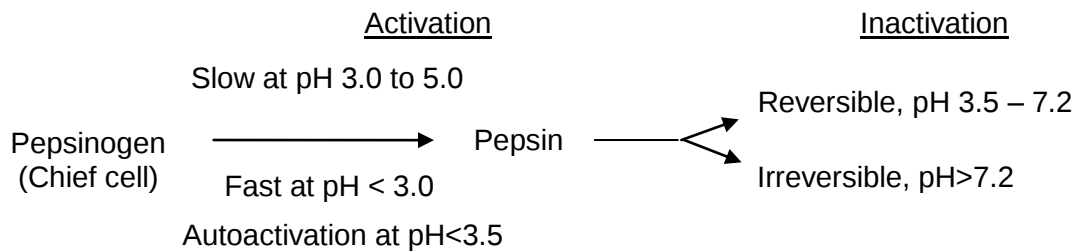
Gastric Secretion of Pepsinogen

➤ Pepsinogen and Pepsin

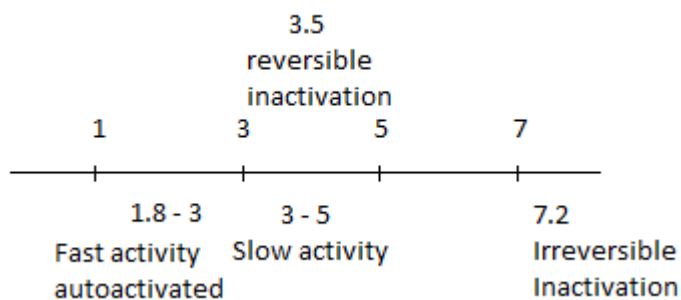
- Chief cells in the gastric body secrete pepsinogen.
- Chief cells have receptors for Ach and secretin.
- Ach is the major agonist of pepsinogen secretion.
- VIP, β_2 -adrenergics, PGE₂ are also agonists of pepsinogen secretion.
- The nitrogenous proteolytic breakdown products of pepsin also stimulate the secretion of gastrin from antral G cells, and CCK from I cells in the duodenum.
- The affinity of the CCKA receptor is higher for CCK than for gastrin, whereas the CCKB receptor has a greater affinity for gastrin than for CCK.
- There are receptors on the chief cells for secretin.
 - M₃ muscarinic receptor for Ach and the CCK_A receptor for CCK.
 - M₃/CCKA stimulate chief cell pepsinogen secretion through an increased intracellular concentration of Ca⁺².

- Pepsinogens are a group of proteolytic proenzymes, (aka “zymogens”). There are three isoforms of gastric pepsinogen.
 - Group I pepsinogens, the main pepsinogen which is secreted from the gastric chief cells located in the body of the stomach.
 - Group II pepsinogens also secreted from chief cells as well as from mucous neck cells in the gastric cardia, body and antrum.
 - The third isoform of pepsinogen is cathepsin E.
- The pepsinogen secretory granules fuse with other secretory granules in the chief cells, and then fuse with the outer plasma membrane of the chief cells.
- Both preformed and newly synthesized pepsinogen are secreted into the gastric lumen by this process of compound exocytosis.
- The pepsinogen secreted into the gastric lumen is an inactive enzyme precursor, which must be activated before it has proteolytic activity and can begin to digest protein.
- Pepsin is the active proteolytic component of pepsinogen.
- The endopeptidase pepsin breaks down dietary protein into relatively large peptides.
- While most protein digestion occurs in the duodenum as the result of pancreatic trypsin, gastric pepsin still plays an important role as an endopeptidase,
- Autoactivation of pepsinogen by pepsin
 - At gastric pHs of between 3.0 to 5.0, there is slow cleavage of a small terminal fragment of pepsinogen to form pepsin.
 - At pH less than 3.0, the activation of pepsinogen to pepsin is very fast.
 - Pepsinogen is also “autoactivated” by pepsin at pH <3.5.
 - At pH 3.5 to 1.8, the pepsin is highly proteolytic.
 - If the pH rises above 3.5, the pepsin becomes reversibly inactivated.

- If the gastric pH exceeds 7.2, the pepsin enzyme activity is destroyed (irreversible inactivation).



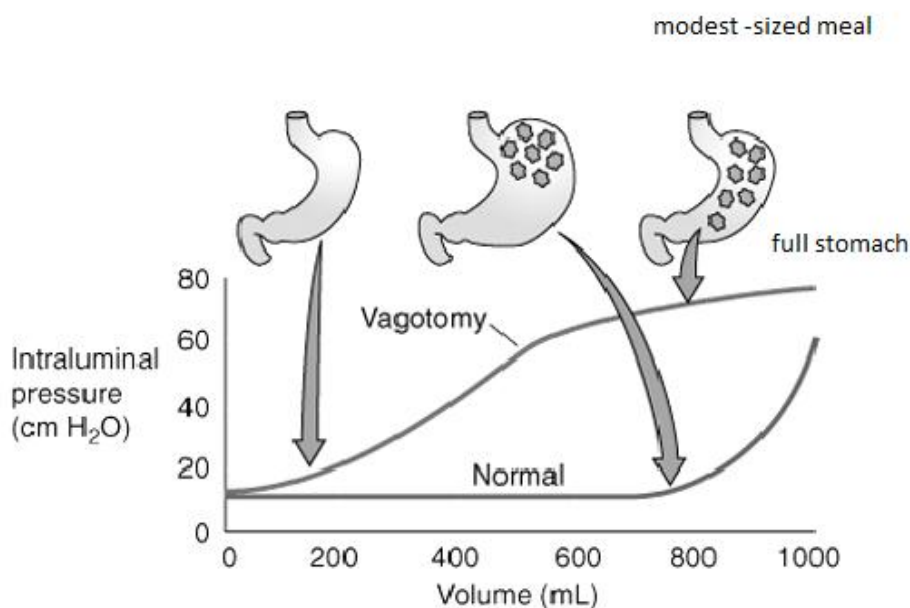
Gastric Filling and Emptying



Overview

➤ Gastric Accommodation and Receptive Relaxation

- Receptive relaxation for liquids is in the fundus, as occurs with solids, as well as in the gastric body and antrum.
- With the intake of food/fluid, the stomach initially stretches, without any increase in its basal intraluminal pressure of about 10 cm H₂O.
- This “accommodation” of intragastric volume is mediated by the afferent and efferent pathways of the vagus nerve.
- Relaxation is effected through stimulation of an inhibitory, nitrergic neuron.
- The inhibitory motor neuron may also be stimulated by Ach and serotonin.



- The mechanoreceptors are also stimulated by
 - IM-ICCs in wall of the fundus
 - Vagovagal reflexes
 - Activated vagal afferent neurons
 - Distention of antrum, duodenum, colon
 - Chemicals in lumen: lipid, protein or H⁺ in duodenum
- Gastric enterochromaffin cells release serotonin (5-HT).
- 5-hydroxytryptamine-3 (5-HT₃), GRP (gastrin-releasing peptide), and CCK_A receptors act on the capsaicin-sensitive gastric afferent vagal nerves.
- 5-HT activates gastric IPANs (intrinsic primary afferent neurons) in gastric submucosal and myenteric plexus.
- IPANs signal afferent vagal neurons (vasovagal reflex) and also signal reflexes and SNS (sympathetic nervous system).
- Afferent vagal neurons connect to nodose ganglia (cell bodies) and NTC (nucleus tractus solitarius), as well as to ICCs connecting to circular muscle.

- NTC connect to hypothalamus and cortex.
- Pain stimulates splanchnic / spinal primary afferent neurons.
- These primary afferent neurons connect to dorsal horn of spinal cord, and from there to spinothalamic and spinoreticular tracts in dorsal column.
- The afferent vagal neurons and the vagovagal reflexes involve
 - Nucleus of tractus solitarius
 - Vagal dorsal motor nucleus
 - Vagal efferents
- NO and VIP (vasoactive intestinal peptide) are released and stimulate the vagal inhibitory neurons.
- The vagal excitatory neurons are inhibited

➤ Gastric Emptying

- To understand the complex, integrated process of gastric emptying, consider gastric accommodation, MMCs and fasting, antral filling and the pyloric pump

➤ Gastric Accommodation

- Migrating myoelectrical (or “motor”) complex, MMC, phase I, II, and III
- Antral filling
- Antral peristalsis; pyloric and duodenal resistance, and co-ordination of the antrum, pylorus and duodenum.

➤ MMCs and Fasting

- MMC I
 - no activity
- MMC II
 - irregular, random contractions

- MMC III
 - 5 to 10 min regular bursts of high amplitude phasic contraction occurring at a rate of 3 per min
 - Motilin is involved in the initiation of MMC III
 - MMC I to III recur every 90 to 120 min
 - MMCs originate in the stomach / duodenum and travel to the ileum.
 - MMCs begin and continue through non-vagal mechanisms.
 - MMCs occur in other parts of GI tract besides stomach and duodenum: LES, sphincter of Oddi, gallbladder.
- Antral Filling and Pyloric Pump
- The food contents of the fundus are mixed with saliva, gastric acid and pepsin.
 - The body and antral peristaltic waves grind the food into 1- to 2- mm solid particles (trituration).
 - The period of grinding of solid food into small particles before emptying begins in the lag period.
 - Antral peristalsis occurs at the rate of 3 per minute.
 - With co-ordinated relaxation of pylorus, 2-4 ml of chyme containing the 1- to 2- mm solid particles are emptied into the pylorus, usually in little pulsatile.
 - The amount of material emptied across the pylorus (“stroke volume”) is set not by volume but by calories.
 - The rate of caloric emptying is 3 to 4 kcal/min.
 - This caloric emptying rate, and the rate of emptying of the volume which contains the calories, is determined by
 - The amplitude (normally 10 to 40 mm Hg) and length of the peristaltic contraction
 - Intra-gastric pressure
 - The pressure gradient across the pyloric sphincter

- Some gastric peristaltic contractions may push chyme into the antrum, and then stop.
- Other peristaltic contractions continue to the pylorus.
- If the pylorus is closed, the chyme pushed as far as the pylorus will return to the gastric body for more grinding (mixing, tituration).

Determinants of Rate of Gastric Emptying

- The time for gastric emptying or the half-time ($t_{1/2}$) for emptying, depends upon a number of factors, including amount and composition of the ingested food.

➤ Food-related factors

Response to Ingestion of Liquids

- Receptive relaxation for liquids is in the fundus, as occurs with solids, as well as in the gastric body and antrum.
- Liquids are emptied faster than solids
 - Liquids do not require grinding before passing through the pylorus.
- Water empties faster than calorie-dense liquids

Response to Ingestion of Solid Food

- With the intake of food/fluid, the stomach initially stretches, without any increase in its basal intraluminal pressure of about 10 cm H₂O.
- This “accommodation” of intragastric volume is mediated by the afferent and efferent pathways of the vagus nerve.
- Relaxation is effected through stimulation of an inhibitory, nitroergic neuron.
- The inhibitory motor neuron may also be stimulated by Ach and serotonin.
- When the volume of the stomach distends beyond the ability of the stomach to accommodate (usually about 800 ml), the intragastric pressure rises, and the person may begin to feel “full”.

- Gastric emptying is influenced by
 - Food
 - Calorie density
 - Viscosity
 - Acidity
 - Contents of fat > protein > carbohydrate
 - Osmolality
 - Fiber
 - Tryptophan
 - Volume
 - Fatty acids in duodenum or ileum
 - Motility
 - Hormones
 - GLP-1
 - CCK and the “duodenal break”
 - CRF and AVP
- The Motility-related Factors
 - Fundic accommodation
 - Antral peristaltic contraction characteristics
 - The pressure gradient between stomach and duodenum
 - The degree of antropyloroduodenal coordination
 - Pylorospasm
 - Presence of dysmotility (e.g., tachygastria)
 - The amount of duodenogastric reflex
- Hormone Related Factors
 - Peptides CCK, CCK_A receptors, GLP-1, PYY, CRF, dopamine, and glucagon.

- GLP-1 (glucagon-like polypeptide -1)
 - GLP-1 is released in proportional response to hyperglycemia.
 - Hyperglycemia releases insulin (incretin effects of GLP-1), which causes
 - ↓ antral contractions
 - ↑ gastric dysrhythmias
 - ↓ sensation of fullness from fundic distention
 - ↓ gastric emptying
 - Hypoglycemia and GLP-1 or hyperglycemia (> 220 mg/dL)
 - ↑ dysrhythmias
 - ↑ contractility
 - ↑ emptying
 - ↑ dysrhythmias
- CCK and the “Duodenal Break”
 - Fatty acids in the ileum stimulate an enterogastric reflex (the “ileal break”) to slow gastric emptying.
 - The ileal break involves PYY, CCK and GLP-1.
- BMI
 - As BMI increases, gastric emptying becomes faster
 - Medium- and long- chain fatty acids release CCK.
 - CCK slows gastric emptying
 - ↓ fundic tone
 - ↓ antral contraction
 - ↑ pyloric tone
 - CCK activates CCK_A receptors on the vagal afferent neurons.
 - Vagal afferent neurons ascend to the nucleus tractus solitarius (NTS).

- Nerves from NTS ascend to the periventricular nucleus (PN).
- PN participation leads to satiety.
- Vagal dorsal motor nucleus (DMN-V) connect to descending vagal efferent neurons.
- Descending vagal efferent neurons reduce gastric emptying.
- The net effect of CCK is to inhibit gastric emptying.
- This represents the duodenal “brake”
- CRF and AVP
 - As part of the stress response gastric emptying slows from
 - CRF (corticotropin-releasing factor)
 - AVP (vasopressin) acts on pathways in PN
 - Acts through central dopamine 1 and 2.

Tests of Gastric Neurological Function

- Emptying
 - Scintigraphy
 - Capsules technology
 - Breath tests
 - Volume recovery tests
 - Ultrasonography
 - CT/MRI technology
- Antral contractions
 - Antroduodenal manometry
 - Capsule technology
- Myoelectrical activity

- EGG (electrogastrography)
 - Tachygastrias (> 3.7 cpm)
 - Bradygastrias (< 2.5 cpm)
- Gastric relaxation
 - Barostat
 - Measurement of intragastric tone and volume (not pressure)
 - SPECT – single photon emission CT
 - Scintigraphy, ultrasonography, MRI

Pathophysiological Defects and Pharmaceutical Approaches in Diabetic Gastroparesis

Symptoms	Pathophysiology	Pharmaceutical approaches
➤ Early satiety and postprandial fullness	○ Defective accommodation from ↓ in NOS neurons	- NO donors
➤ Nausea and vomiting	○ Gastroparesis secondary to enteric nervous system neuropathy ○ Abnormal pacemaker activity	- Prokinetic agents - Gastric - ↓ pacing
➤ Epigastric pain	○ Sensory neuropathy in gastric wall	- Tricyclic antidepressants - Neurostimulation
➤ Persistent nausea	○ Tachygastria / bradygastria from abnormal pacemaker activity	- Control of blood glucose - Domperidone

Adapted from: Owyang C. *Gastroenterology* 2011;141:136

CLINICAL PHYSIOLOGICAL CHALLENGE - Gastroparesis

Case: A 28 year old diabetic man with poor insulin control of his hyperglycemia presents with post-prandial nausea, fullness and discomfort. He is diagnosed as having diabetic gastroparesis.

Question:

- c) Give 6 tests of gastric neurological function which might be used in this patient to document the suspected presence of gastroparesis.
- d) What are the pathophysiological defects which occur in diabetic gastroparesis, the resulting symptoms, and the potential pharmaceutical approaches to help correct the defects and relieve the symptoms?

Vomiting

- Trigger areas for vomiting include
 - CNS: Drugs such as digitalis and some cancer chemotherapeutic agents activate the area postrema in the brain.
 - Inner ear dysfunction or motion sickness acts through the vestibular nerve and vestibular nuclei.
 - Pharynx
 - Coronary arteries
- GI tract, bile duct, peritoneum: These triggers from the GI tract acts by vagal afferent pathways, presumably to rid the body of the irritant.
- Nausea is the sensation that vomiting may occur, and often proceeds vomiting which arises from disorders in the GI tract.
- Vomiting arises from series of multiple afferent stimuli coordinated by one or more brain centers.
- These multiple afferent stimuli lead to a coordinated neuromuscular response involving several preprogrammed coordinated smooth and striated muscle responses.
- Other trigger areas include
 - Pharynx
 - Peritoneum

- Bile ducts
- Cortex, thalamus, hypothalamus
- There are CNS and GI components to vomiting.

➤ CNS

- The primary locus to receive emetic stimuli is the area postrema, (aka the chemoreceptor trigger zone [CTZ])
- The nucleus tractus solitarii in the brainstem plays an important role in the initiation of emesis.
- Neurotransmitter receptors that are important in various causes of vomiting include:
 - Brain: neurokinin NK₁ and substance P receptors in the nucleus tractus solitarii,
 - GI tract: 5-HT₃ receptors in vagal afferents,
 - Vestibular nucleus: dopamine D₂ receptors in the vestibular nucleus.

➤ GI

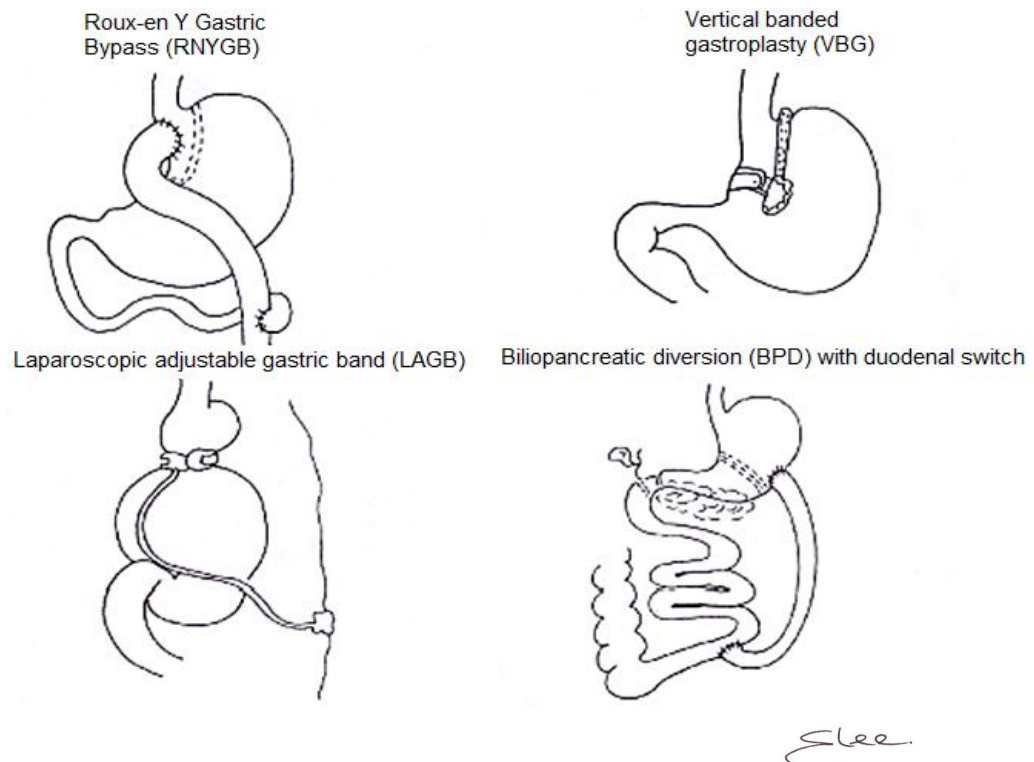
- The initial event leading to vomiting is the loss of intestinal slow-wave activity.
- The loss of this slow wave activity is linked to propulsive peristaltic contractions.
- The normal peristaltic contractions of the stomach and small intestine decline, and are replaced by retrograde contractions, beginning in the ileum and progressing upwards towards the stomach.
- These retrograde contractions are accompanied by contraction of the external intercostal muscles and the diaphragm against a closed glottis.
- The Valsalva-like action increases intra-abdominal pressure.
- The diaphragmatic crural muscle and lower esophageal sphincter relax
- The increase in intra-abdominal pressure forces the gastric contents up into the esophagus.

- The larynx moves upward and forward, and UES (upper esophageal sphincter) relaxes.
- Gastric contents are vomited.
- The closed glottis protects the airway and prevents aspiration.

Gastric Surgery

- Resection of a portion of the stomach is still performed in some persons with complicated peptic ulcer disease, for gastric cancer, or for weight reduction (bariatric surgery).
- While all types of gastric surgery are prone to the development of late complications, these are more prevalent, if there is an afferent loop, such as with a Billroth II procedure (antrectomy, vagotomy and afferent loop), or a Roux-en-Y hepaticojejunostomy.

➤ Types of Bariatric Surgery for Weight Loss Operations



Adapted from: *Slisenger and Fordtran's Gastrointestinal and Liver Disease*.
Figure 7-1, Page 116, Ninth Edition, 2010.

CLINICAL PHYSIOLOGICAL CHALLENGE

Question: Draw the anatomy for three of the bariatric surgical procedures used for weight loss

Answer: See Figure above

CLINICAL PHYSIOLOGICAL CHALLENGE – Gastroparesis

Case: A 29 year-old diabetic lady develops bloating and fullness after meal. She diagnosed with possible gastroparesis, and is referred to you for management. You recommend alterations in her diet, and explain her choices of prokinetic agents.

Questions:

- What is the pathophysiology of gastroparesis (not just in this patient)?
- What is the basis for the dietary recommendations which you make?
- What are the receptors on smooth muscle which may be targeted for her pharmaceutical treatment?

CLINICAL PHYSIOLOGICAL CHALLENGE - Malabsorption

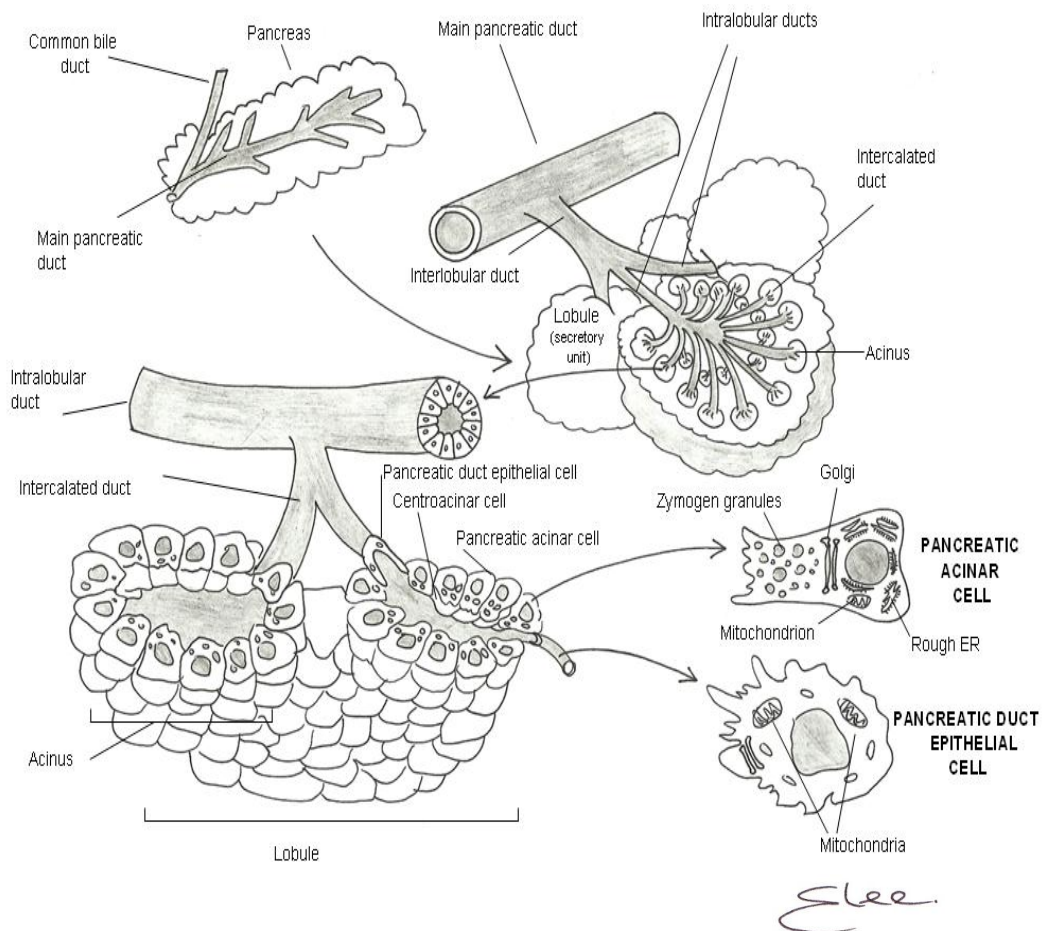
Case: A 65 year old man had a Billioth II gastric resection 25 years ago for failed ulcer healing when treated with an H_2 – receptor antagonist. He presents to you now with anemia and diarrhea. The stools are malodorous, and float.

Questions:

- What are the mechanisms for the digestion of iron- and vitamin B12 – containing foods?
- How are these normal processes deranged after gastric surgery?
- Give the pathophysiology of the diarrhea and steatorrhea which may arises as a result of gastric surgery.

PANCREAS

Functional Anatomy of the Pancreas



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 43-1, page 913.

- From 15 to 100 acinar cells form an acinar cluster.
- Acinar cluster connects the acinar lumen to an intercalated duct. Multiple intercalated ducts join the intralobular ducts.
- The intralobular ducts join the interlobular duct, and then the main pancreatic duct.

- The cells at the junction of the acinus and the intercalated ducts are cuboidal centroacinar cells. These as well as the proximal intercalated duct cells have many mitochondria to facilitate salt and water secretion.
- The more distal intercalated ducts are lined by larger cuboidal cells containing cytoplasmic vesicles and granules, which facilitate the secretion of both alkaline fluid and proteins.
- The average amount of pancreatic juice produced daily contains 15-100 g of protein (in fact, the pancreas has the body's highest rate of daily protein synthesis and secretion).
- Acinar cells secrete enzymes (protein), as well as isotonic NaCl-rich fluid.
- This acinar fluid represents about a quarter of the total fluid secreted by the pancreas gland.
- The other 75% of the fluid secreted is HCO_3^- rich fluid from the pancreatic duct cells.
- The HCO_3^- in the duodenal lumen helps to neutralize the acidic "squirts" of the mixture of the 2 mm particles of food as well as gastric acid which leaves the stomach as the result of antral contraction and the coordinated relaxation of the pylorus.

Pancreatic Acinar Cell Secretion of Protein (Proenzymes & Enzymes)

Basal Secretion

- With fasting (the interdigestive period), there is only a low level of basal (or constitutive secretion [CS]) of protein by the acinar cells).
- The basal secretion from the stomach, biliary tree and pancreas vary in relation to the four phases of the small intestinal MMC (migrating motor complexes). In phase I of the MMC, intestinal motility is minimal, and so also are the basal gastric, biliary and pancreatic secretions.
- Duodenal motility increases in phases II and III of the MMC, and this is associated with increased interdigestive period secretion.
- As the MMC motor activity falls in phase IV back to the inactive phase I, pancreatic secretion also falls.

- This cyclic pattern of fasting and fed-associated pancreatic secretion is partially affected by the parasympathetic and the sympathetic autonomic (α -adrenergic tone) systems, as well as through the hormonal effects of CCK during MMC phases I and II.

Stimulated Secretion

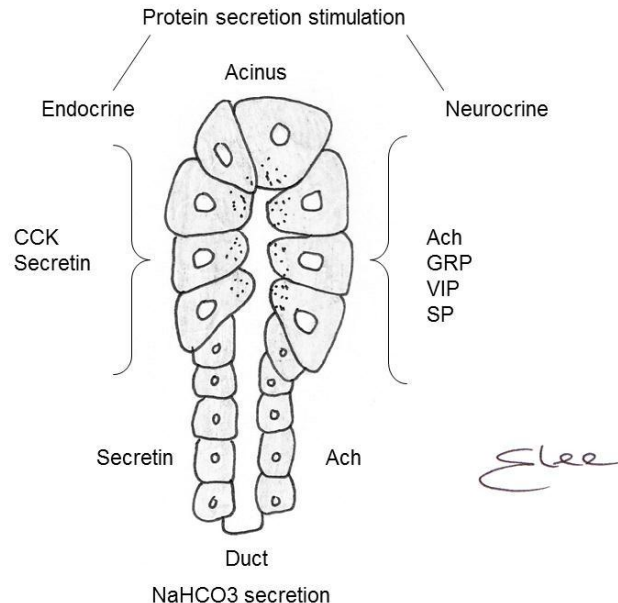
The Macro' Level of Pancreatic Secretion

Cephalic phase: vagal afferents and efferents

- This cephalic phase of pancreatic secretion contributes between 10 to 20% of the maximal daily pancreatic enzyme secretion.
- The pancreatic secretion of protein, fluid and electrolytes is coordinated in both a stimulatory and inhibitory manner by the cephalic, gastric, and intestinal phases.
- The cephalic phase of pancreatic secretion begins with the sight, smell and taste of food.
- This vagal afferent sensory information is integrated in the dorsal vagal complex (DVC) of the hypothalamus, as well as on the mammillary bodies.
- With this neuroluminal stimulation resulting from the intake of food, there is regulated secretion (RS; 5-10 times > CS [Constitutive secretion, aka basal secretion]).
- Once the DVC has integrated the vagal afferents, the vagal efferents are then activated.
- The pancreatic ganglia release the neurotransmitters Ach, GRP (gastrin-releasing peptide) and VIP.
- Ach, GRP and VIP increase acinar cell Ca^{2+}_i (intracellular concentration of Ca^{2+}).
- These neurotransmitters bind to their individual receptors on the acinar cell.
- CCK, GRP, VIP increase acinar cell Ca^{2+}_i .

- PTF-1 (pancreatic transcription factor) binds to the PCE (pancreatic consensus element) in the enhancer regions of the 5' flanking nucleotide sequences
- This regulates the transcription of the mRNAs for the synthesis of the pancreatic digestive enzymes and coenzymes.
- The endocrine regulation of pancreatic secretion by the acinus is mediated by CCK and secretin.
- The efferent pathways of the vagus nerve release Ach, GRP and secretin to begin both gastric and pancreatic secretion through the activation of M3 receptors on both the gastric parietal and pancreatic acinar cells to release digestive enzymes, and to lesser extent to stimulate ductular cells HCO_3^- and fluid.
- This pancreatic secretion of water and electrolytes (especially HCO_3^-) provides partial alkalization of gastric HCl entering the duodenal lumen.

NEUROENDOCRINE AND ENDOCRINE REGULATION OF PANCREATIC ACINAR AND DUCTULAR SECRETION

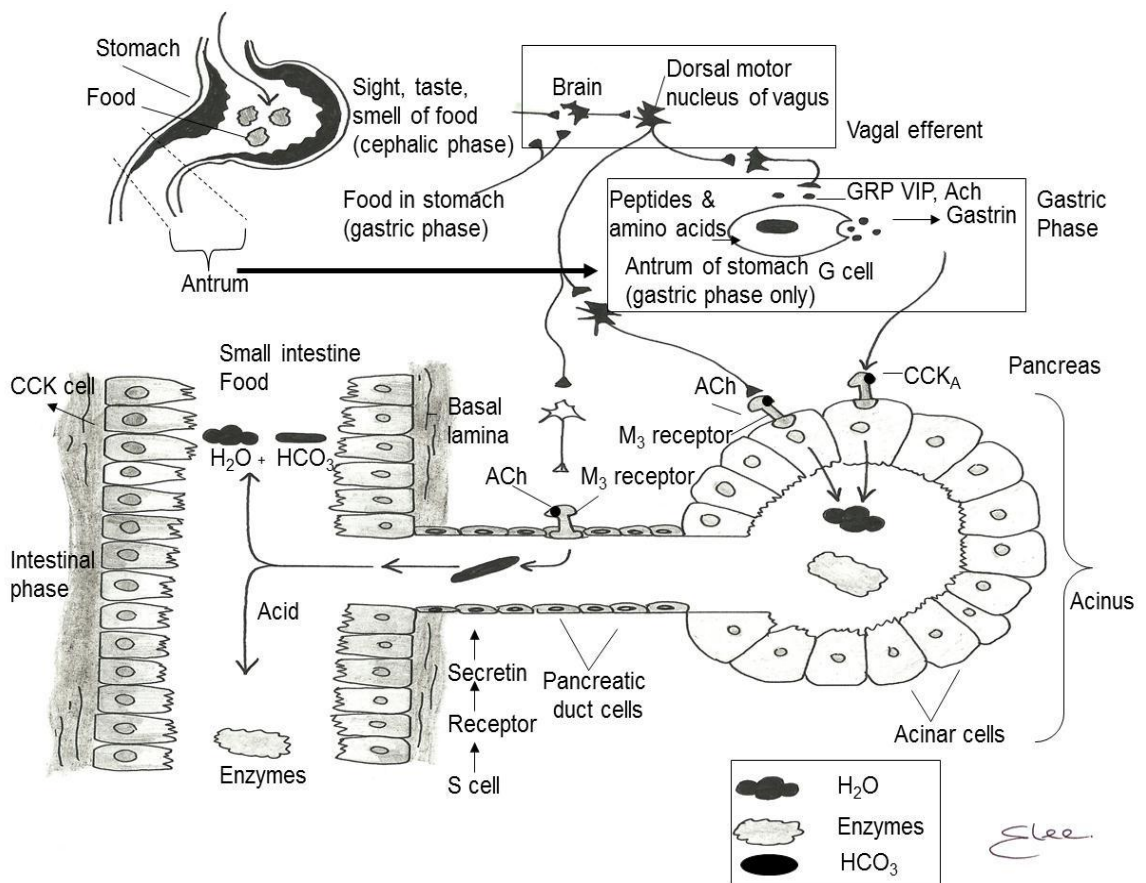


Abbreviations: Ach, acetylcholine; CCK, cholecystokinin; GRP, gastrin-releasing peptide; SP, substance P; VIP, vasoactive intestinal peptide

Adapted from: *Slisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 56-1, page 922, Ninth Edition, 2010

- The effect of the cephalic phase on pancreatic fluid secretion is much less than on the enzyme secretion.
- As a result, the enzyme concentration in pancreatic juice is high during the cephalic phase (because of the relatively high enzyme content and low fluid volume).

CEPHALIC AND GASTRIC PHASE OF PANCREATIC SECRETION



Abbreviation: DVC, dorsal vagal complex

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 43-9, page 924.

- **Gastric phase**

- The gastric phase of pancreatic secretion contributes between 50 to 80% of maximal daily pancreatic secretin enzyme secretion.

- **Acetylcholine**

- The distention of the stomach by ingested food and fluid stimulates the stomach to release Ach through cholinergic vagal pathways.
- Acetylcholine (Ach), secretin, cholecystokinin (CCK), gastrin-releasing peptide (GRP), and vasoactive intestinal peptide (VIP) act as neural and humoral agonists.
- Ach acts through an M3 receptor to activate the pancreatic and the ductular cells to activate the pancreatic acinar and ductular cells.

- **Gastrin**

- Semidigested food peptones and amino acids (especially valine, methionine and phenylalanine) release gastrin from the antral and duodenal G-cells.
- Gastrin is a relatively poor agonist of the CCK_A receptors on acinar cells.

- **Intestinal Phase**

- The digestive capacity of the pancreatic enzymes for carbohydrates, proteins, nucleic acids and lipids becomes even greater with the alkalization of the duodenal contents by the ever-increasing pH (alkalinization) of the luminal contents achieved by the higher rates of HCO₃⁻ secreted into pancreatic fluid, and thereby the neutralization of the squirts of gastric acid entering the duodenum.
- This partial alkalinization of the duodenal lumen provides the necessary environment for the activation of the pancreatic proenzymes in the zymogen granules (trypsinogens, chymotrypsinogen, proelastase, protease E, precarboxypeptidase A and B).

- This duodenal alkalinization reduces the acid-associated stimulation of the duodenal D cells which release secretin; thereby, this becomes a negative feedback loop.

➤ Secretin

- It is essential to achieve the pH optimum for activation and activity of pancreatic enzymes: this is the importance of secretin.
- Acidic chyme entering the duodenum from the stomach is the major stimulant of pancreatic secretion of protein- and HCO_3^- - rich fluid.
- With the arrival of acidic chyme in the duodenum, S cells release secretin, which stimulates the secretion of alkaline (HCO_3^- - containing) pancreatic fluid from the duct cells.
- The HCO_3^- partially neutralizes the gastric acid emptied into the duodenum.
- Secretin (and VIP) increase cAMP in the acinar and ductular cells.
- Recall that fatty acids in the duodenum also reduce gastric acid secretion, slow gastric emptying, and stimulate pancreatic HCO_3^- rich ductular secretion.

➤ CCK

- Peptides, amino acids and fatty acids in duodenal lumen release
 - CCK from the basolateral membrane of duodenal mucosal I neuroendocrine cells, and
 - CCK-RF (CCK-releasing factor protein)
- Because CCK is released from the I cells and acts in a paracrine or endocrine manner, it is not subject to proteolytic destruction.
- Because some of these CCK-releasing factors are proteins, and because these proteins are secreted into the duodenal lumen, they are subject to breakdown by the pancreatic proteolytic enzymes (e.g., trypsin).
- Thus, CCK-RF are trypsin-sensitive proteins.

- These CCK-releasing factors (CCK-RF) do not play as important a role as does CCK itself on pancreatic acinar cell secretion of pancreatic enzymes.
- CCK activates vagal afferent neurons.
- Protein and lipid breakdown products also stimulate vagal neurons .
- The vagal afferent neurons initiate a vagovagal reflex that primarily stimulates the acinar cells through M3 cholinergic receptors.
- CCK binds to its receptor on the acinar cell, and causes the release of pancreatic digestive enzymes and proenzymes from the acinar cells.
- CCK, GRP and Ach increase acinar cell Ca^{2+} (intracellular calcium, Ca^{2+}) concentration, whereas VIP and secretin increase cAMP.
- CCK stimulates acinar cell protein and fluid (NaCl-rich) secretion.
- CCK-RF (CCK-releasing factors)
 - CCK-RF factor may contribute to CCK release in the interdigestive phase, as well as after a meal (digestive phase).
 - Under basal conditions, there is little trypsin to inactivate CCK-RF.
 - With the ingestion of nutrients which are substrates for trypsin, trypsin digests the CCK-RF as well as ingested food.
 - Less CCK-RF is broken down, so more CCK-RF is available to stimulate CCK secretion.
 - Depending upon the balance between the proteins and lipids in the duodenal lumen, (both of which stimulate secretion of CCK and CCK-releasing factors), and the proteolytic enzymes breaking down the CCK-releasing factors, there may be more or less of these CCK-releasing factors.
 - Thus, releasing factors (RF) secreted from the intestine are responsible for negative feedback regulation of pancreatic secretion.

- There is regulation of these mRNAs for pancreatic enzymes in response to enrichment of the dietary nutrient load: ↑ carbohydrates, ↑ amylase; ↑ fat, ↑ lipase.

Gastrointestinal Peptide Hormones Acting on on Pancreas and Gallbladder

Hormone	Source	Action
➤ Pancreas		
○ Cholecystokinin (CCK)	I cells in duodenum and jejunum and neurons in ileum and colon	↑ Enzyme secretion
○ Secretin	S cells in small intestine	↑ HCO_3^- and fluid secretion by pancreatic ducts
○ Gastric inhibitory peptide (GIP)*	K cells in duodenum and jejunum	Exocrine: ↓ fluid absorption ← ↓G, ↓HCl Endocrine: ↑ insulin release
○ VIP	ENS neurons	↑ Secretion by pancreas
○ Somatostatin (SST)		↓ Endocrine/exocrine secretions
○ PYY	Endocrine cells in ileum and colon	↓ Enzyme and fluid secretion
➤ Gallbladder		
○ CCK	I cells in duodenum and jejunum, and neurons in ileum and colon	↑ Contraction

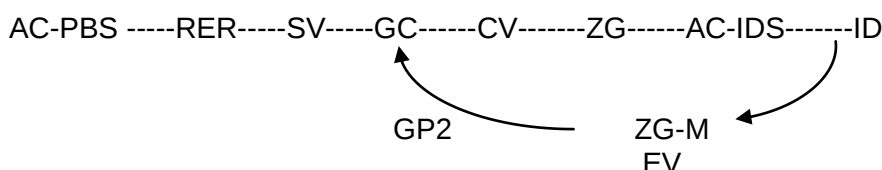
*GIP is also known as “glucose-dependent insulintropic polypeptide”

Abbreviations: PPP, peptidergic postganglionic parasympathetic neurons

Printed with permission: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Table 41-1, page 889.

Hormone	Cell Secretion	
	Acinar	Duct
CCK	↑	
Secretin		↑
VIP		↑
PYY	↓	↓
SST	↓	↓

The Micro' (Cellular) Level of Pancreatic Secretion of Enzymes



Abbreviations: AC-IDS, apical – intralobular duct side; AC-PBS, apical cell – portal blood side; CV, condensing vacuole; EV, empty vesicle; GC, Golgi complex; ID, intralobular duct; RER, rough endoplasmic reticulum; SV, small vesicle; ZG, zymogen granule; ZG-M, zymogen granule membrane

- The pancreatic acinar cells are the main source of secretion of enzymes.
- The pancreatic acinar cells are the main source of secretion of water and
- However, the acinar cells secrete small amounts of water and electrolytes, and the duct cells secrete small amounts of enzymes.
- Synthesis of enzymes and proenzymes, and trafficking of vesicles to the apical membrane of the acinar cell.
 - The acinar cells take up amino acids from the portal blood.
 - In the acinar cells, the rough endoplasmic reticula (RERs) synthesize nascent proteins.

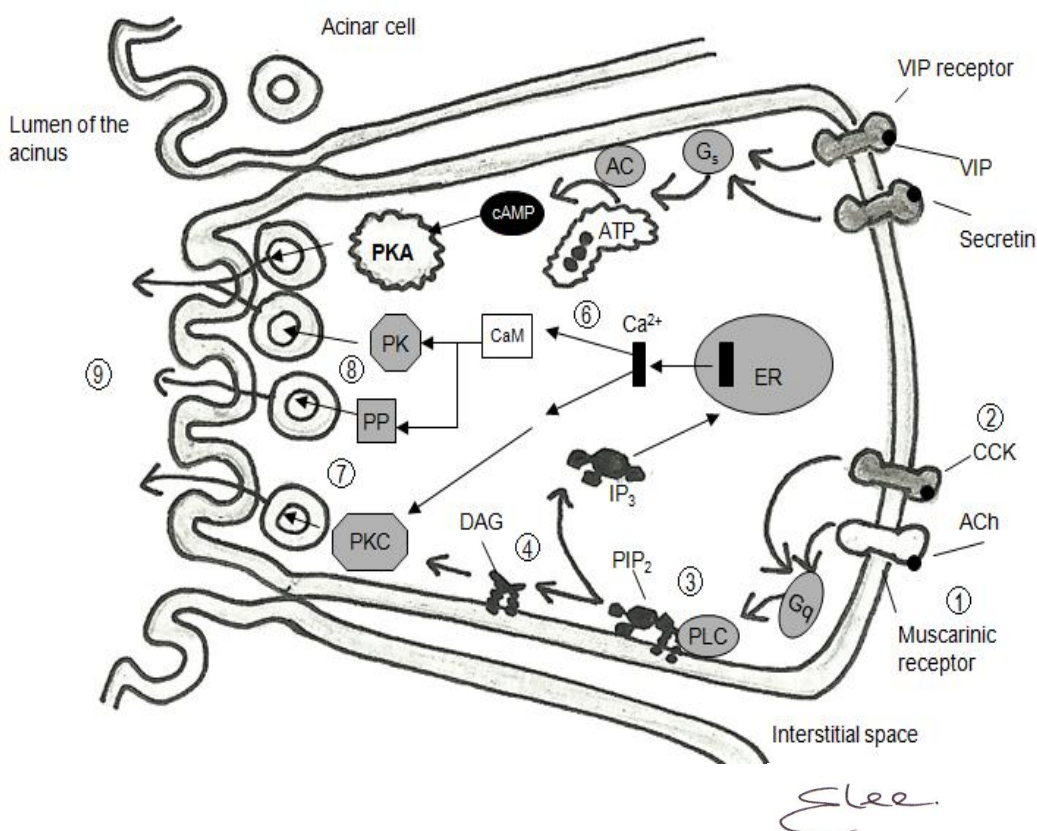
- The nascent proteins form small vesicles in RERs.
- These small vesicles leave the RER's and traffick to the Golgi complex.
- The normal extracellular proteolysis is important for digestion of food protein or protein breakdown products in the duodenal lumen.
- The proteolytic enzymes of the acinar cells have the potential to digest themselves (autodigestion).
 - pancreatic fluid secretion, and
 - by the mixing of the enzymes with food in the intestinal lumen
- Normally, the lysosomal enzymes of the Golgi complex would break down these newly synthesized proteins.
- The pancreatic proteins destined to be secreted as enzymes lack the mannose 6 phosphate receptor.
- Because these pancreatic proteins lack this mannose 6 phosphate receptor, they are not broken down by the lysosomal enzymes in the Golgi complex.
- Proteins leave the Golgi complex in the cytoplasm of the acinar cells in large membrane-bound structures, the condensing vacuoles.
- The proteins in the condensing vacuoles become densely packed and further condensed, and are surrounded by membrane, pinched off and secreted as smaller "zymogen granules".
- The zymogen granules traffic to the inner surface of the apical membrane of the acinar cell, where the membrane of the secretory zymogen granules temporarily fuses with an area of the apical plasma membrane of the acinar cells.
- The inactive proenzymes in the secretory zymogen are released into the lumen of the intralobular ducts of the pancreas.
- The membrane of the zymogen granule detaches from the apical membrane of the acinar cell.
- The acinar cell membrane shrinks, and becomes "resealed".

- Trafficking of empty vesicles back to the golgi of the acinar cell: GP2
 - The zymogen granule minus its membrane becomes “empty” zymogen granules.
 - The acinar cell also secretes the protein GP2.
 - GP2 binds to the inner leaflet of the membrane of the zymogen granule membrane.
 - The GP2 bound to the inner membrane of the emptyzymogen granule aids the trafficking of these membranes back to the Golgi of the acinar cells.
 - These “empty” zymogen granules now form new condensing vesicles which contain more inactive enzymes.
 - The recycling continues with the shutting of the zymogen granules and membranes back and forth between the Golgi and apical membrane of the acinar cell.
- Autophagosomes
 - Some trypsinogen-containing zymogen granules that are not secreted from the apical membrane of the acinar cell can be taken up by autophagosomes for removal.
 - These autophagosomes fuse with lysosomes to form autolysosomes in the autolysosomes in the contents of the granules, including proteolytic pancreatic enzymes, are degraded by lysosomal enzymes, preventing their release.
- Neurotransmitters
 - The neural pathways controlling the primary enzyme-rich acinar secretion, and the HCO_3^- -rich pancreatic epithelial ductular cells, are the postganglionic parasympathetic and sympathetic nerves.
 - These nerves, when stimulated, release neurotransmitters (cholinergic, adrenergic and peptidergic).
 - The cholinergic, adrenergic and peptidergic neurotransmitters bind to their appropriate receptors on the acinar and ductular cells.
- Monophasic and biphasic dose responses
 - The major receptors stimulating the acinar cells are for Ach and CCK, from which there is a biphasic dose response (initial rise, later fall) with increasing doses of Ach or CCK.

- The initial rate of protein secretion rises, but as the doses of ACh or CCK are increased further, secretion of pancreatic enzymes falls.
- This increase and then decrease in pancreatic enzyme secretion on response to increasing concentrations of ACh or CCK represents the biphasic dose response in enzyme secretion.
- In contrast, with VIP or GRP, there is a monophasic dose-response: an increased protein secretion which reaches a plateau, (and does not fall as with carbachol or CCK in their biphasic dose-response).

➤ Intracellular events

THE PANCREATIC ACINAR CELL SECRETION OF PROTEIN
(ENZYMES AND PROENZYMES)



Abbreviation: CaM, calmodulin

Adapted from: Boron Walter F. and Boulpaepemile L. *Medical Physiology*, Second Edition,. 2009; Figure 43.4, page 916.

- 1) Ach binds to the muscarinic receptor on the basal membrane (BM) of the acinar cell stimulates PLC to release DAG.
- 2) CCK binds to its BM receptor.
- 3) The Ach and CCK receptors on the basolateral membranes (BM) of the acinar cells are linked to the $G_{\alpha q}$ heterotrimeric G protein. Both Ach and CCK receptors activate G_q , stimulate PLC, PKC and increase intracellular Ca^{2+} .
- When acinar cells have been stimulated by peptides such as CCK or VIP, and the hormonal stimulus is removed and then is reapplied, the receptors become desensitized.
- Because of the desensitization of the CCK and VIP receptors, secretion becomes less than what would have been seen with the initial stimulation.
- 4) G_q activates protein lipase C(PLC), forming PIP_2 , IP_3 and DAG.
- 5) DAG stimulates PKC and IP_3 , which release Ca^{2+} from intracellular stores.
- 6) The intracellular concentration of Ca^{2+} ($[Ca^{2+}]_i$) increases.
- 7) $\uparrow[Ca^{2+}]_i$ activates PP and PK.
- 8) $\uparrow[Ca^{2+}]_i$ activates calmodulin, protein kinases (PK) and protein phosphatases (PP).

Pancreatic Enzymes

➤ Enzymes (secreted in their active form)

- Amylase
- Lipase
- Carboxylesterase
- Sterol esterase
- DNase
- RNase

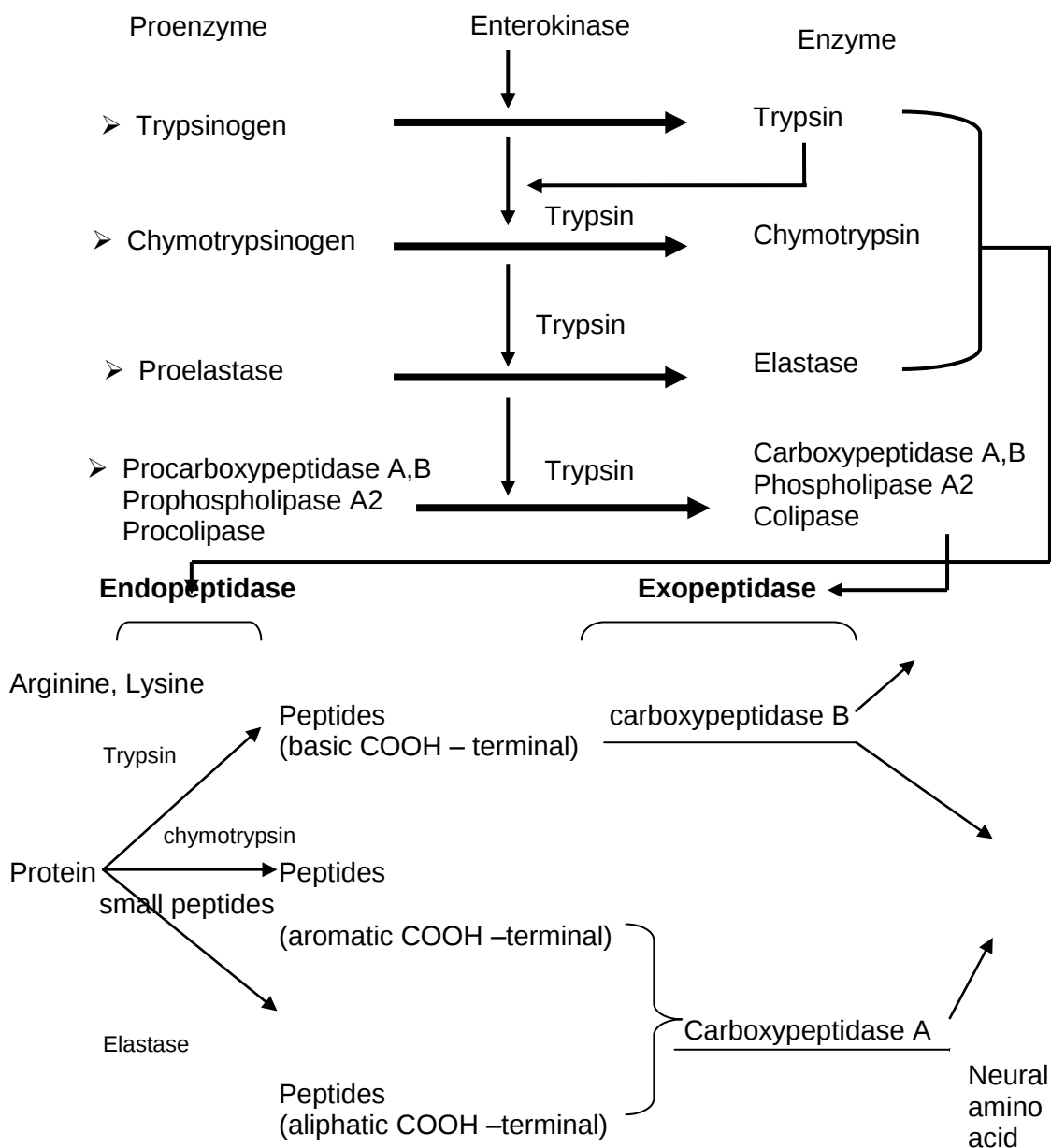
➤ Proenzymes*

- Endopeptidases
 - Trypsinogen
 - Cationic
 - Anionic
 - Mesotrypsinogen
 - Chymotrypsinogen
 - Kallikreinogen
 - Chymotrypsinogen
 - Proelastase
- Exopeptidase
 - Procarboxypeptidase A,B
 - Pyrophospholipase
 - Procolipase

*Inactive enzymes, requiring activation by enterokinase and trypsin

- The pancreatic enzymes digest carbohydrates (amylase), proteins and lipids (lipase, phospholipase, colipase, carboxyl ester lipase), nucleic acids (nucleases, RNAase and DNAase) proteases [secreted as zymogens, requiring activation in duodenal lumen]: trypanogens, dimetrypsinogens, trypsin inhibitor, prolactase, protease E, precarboxypeptidase A and B).

ACTIVATION OF PANCREATIC ENZYMES



- The 3 endopeptidases produce oligopeptides of 2-6 amino acids
- The 2 exopeptidases produce single amino acids.
- Carboxypeptidase A – neutral amino acids and small peptides.
- Carboxypeptidase B – arginine, lysine, and small peptides
- Enterokinase plays an important role in activating trypsinogen to form trypsin.
- Trypsin activates more trypsinogen as well as other proteolytic enzyme proteases.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-14, page 1713, Ninth Edition, 2010

- The more pronounced defect in cathepsin L, which inactivates trypsin, than in the activating enzyme cathepsin B leads to trypsin generation within the autolysosome.
 - Active enzymes are released from these enlarged autolysosomes into the cytoplasm to initiate pancreatic cellular injury.
- VIP and Secretin
- VIP and secretin bind to their receptors on the BM of the acinar cells.
 - VIP and secretin activate Gs.
 - Gs stimulates Ach to produce more cAMP; Ach has only a modest effect on the signaling pathway, and to activate PKA.
 - The PKA, PK, PP and PKC alter the phosphorylation of structured and regulatory proteins to insert the zymogen granule membranes into the apical membrane of the acinar cell.

- In pancreatitis
 - Block in enzymes secretion leads to an accumulation of intracellular zymogen granules, which increases uptake of these structures by autophagosomes.
 - Alternatively, or additively, granules improperly released from the basolateral surface of the acinar cell are taken back up by the cell and sequestered by autophagosomes.
 - Following autophagosome-lysosome fusion, content degradation fails to occur because of decreased levels of cathepsin B and L.
- The mechanisms that protect the acinar cells from autodigestion by its own proteases include:
 - Lysosomal enzymes
 - Prematurely released trypsin may be degraded by lysosomal enzymes through the process of fusion of secretory granules with lysosomes (crinophagy), or through the process of the lysosomes engulfing the secretory granules (autophagia).
 - Autophagosome
 - Enzymes in the lumen and also dilutes by
 - Zymogen granules
 - Packaging of inactive pro-enzymes (trypsinogens, chymotrypsinogen, proelastase) in zymogen granules, which are resistant to intracellular breakdown, and become active only in the intestinal lumen as a result of enterokinase.
 - Trypsin inhibitor
 - The zymogen granules contain pancreatic trypsin inhibitor, which will protect against small amounts (10-20%) of trypsin.
 - This trypsin inhibitor becomes activated before the granules reach the duodenal lumen.
 - Digestive enzymes
 - Any prematurely released trypsin may itself be digested.
 - Trypsin thereby becomes inactive by way of other digestive enzymes in the zymogen granule.

- Dilution of pancreatic juice
 - Fluid secreted from the acinar cells and then from the duct cells dilutes and washes away any prematurely released proenzyme.
 - The overall effect is for Ach to stimulate HCO_3^- secretion by the pancreatic duct cells.
- Loss of stimulated secretion
 - Pancreatic secretion falls after a meal, because of the loss of the cephalic, gastric, and intestinal phases of stimulated secretion.
 - Secondly from the direct inhibitory effects of PYY (peptide YY, released from neuroendocrine cells in the distal small intestine and colon), somatostatin (SST, especially SST-28, released from small intestinal D-cells), and glucagon (released from pancreatic islet [endocrine] α cells) directly inhibit stimulated secretion.
 - Ca^{2+} , PL, and CHOL exit the hepatocytes by means of the MDR1, MDR-2, and ABCG5/ABCG8 transporters in the apical/canalicular membrane.

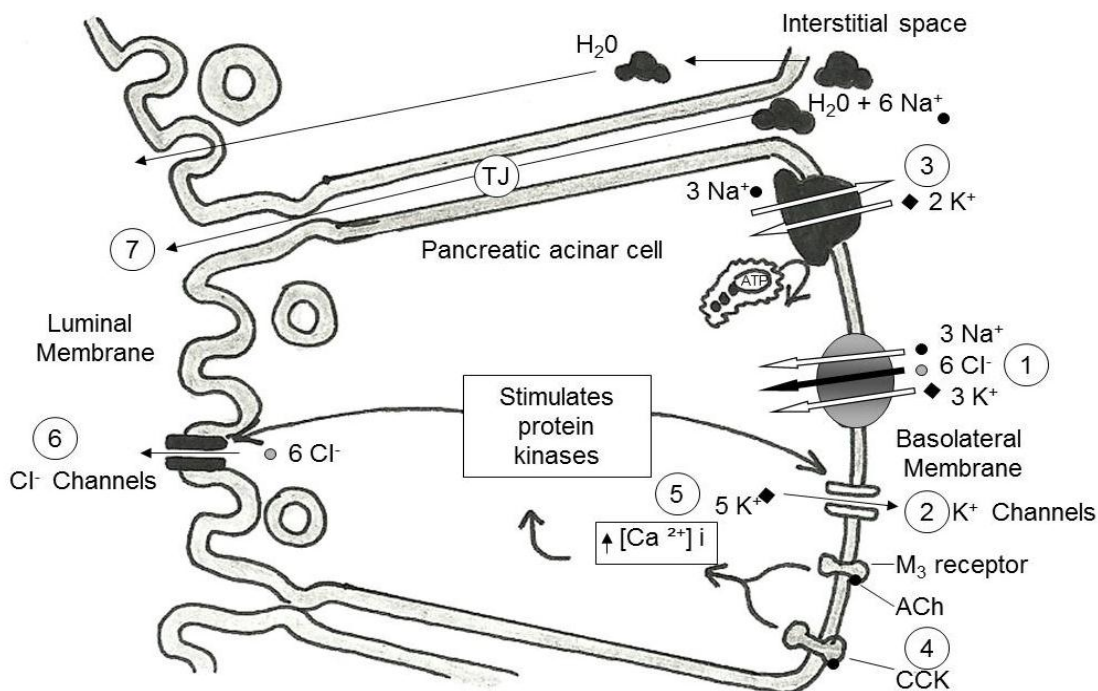
Pancreatic Acinar Cells: Secretion of Water and Electrolytes

CLINICAL PHYSIOLOGICAL CHALLENGE – Pancreatic Dysfunction

Background: When the pancreas becomes chronically inflamed, such as with chronic pancreatitis from alcohol abuse, there is a decrease in enzyme secretion and activity, leading to reduced nutrient digestion, and thereby malnutrition.

Questions: Draw figures to explain the normal processes of pancreatic secretion of enzymes, HCO_3^- and fluid, the control of their secretion, and thereby faulty digestion.

THE PANCREATIC ACINAR CELL SECRETION OF WATER AND NaCl



See

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 43-5, page 917.

The major secretion of water and electrolytes in pancreas is by the duct cells.

- The duct cells secrete a small amount of protein, and acinar cells secrete small amounts of water and electrolytes.
- Pancreatic acinar cells secrete a fluid rich in NaCl, whereas the duct cells secrete a fluid rich in HCO₃⁻.
- Activation of secretion by secretin and ACh increase intracellular cAMP and Ca²⁺ ion.
- cAMP and [Ca²⁺]_i also increase BM K⁺ channel permeability, as well as AM Cl⁻ and HCO₃⁻ channel permeability
- CCK and ACh are bound to high affinity receptors; the released Ca²⁺ activates PKC and calmodulin (CaM)-dependant protein kinases and the acinar cell response increases.

- M3 is the receptor for Ach. There are also receptors on the BM of the acinar cell for VIP, CGRP, somatostatin, secretin, and for insulin. The CCK_A receptor has a higher affinity for CCK than for gastrin, whereas the CCK_B receptor has almost equal affinities for both gastrin and CCK.
- CCK and Ach are bound to low affinity receptors.
- CCK and Ach increases intracellular Ca^{2+} ($[\text{Ca}^{2+}]_i$).
- With high $[\text{Ca}^{2+}]_i$, there are no further oscillations in Ca^{2+} , and therefore no further dose-related secretion by the acinar cells.
- VIP acts through its VIP receptor, increasing the levels of cAMP.
- The increased cAMP, PKA and cGMP influence Ca^{2+} entry and storage in the acinar cell.
- Very high $[\text{Ca}^{2+}]_i$ from this spike of Ca^{2+} in the cytosol of the acinar cell may damage the cytoskeleton, and thereby reduce secretion.
- When both CCK and VIP are present in the circulation, and they have additive effect on acinar secretion.
- CCK transiently and moderately increases the activity of cAMP, and thereby PKA activity.
- High concentrations of CCK cause a prolonged and pronounced increase in cAMP and PKA, as well as NO-assisted increases in cGMP.

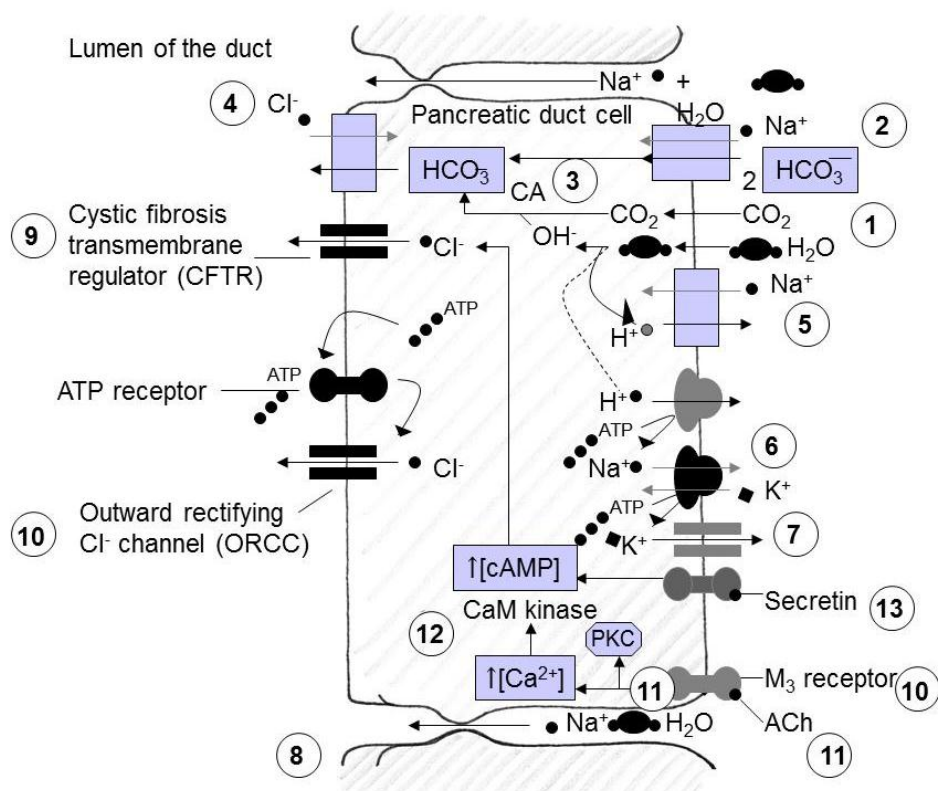
CLINICAL PHYSIOLOGICAL CORRELATION – Pancreatic Fluid

Background: The pancreatic acinar cells secrete some NaCl and water. The apical (luminal) membrane contains Cl^- channels. The basolateral membrane contains Na^+/K^+ ATPase, $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporter and K^+ channels.

Problem: With these membrane components, draw a diagram which depicts the steps in the pancreatic acinar cell secretion of NaCl and fluid.

Pancreatic Duct Cell Secretion of Water and Electrolyte

HCO_3^- SECRETION BY THE PANCREATIC DUCT CELLS



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 43-6, page 919.

Pancreatic Duct Cell Secretion of Water and HCO_3^- (as well as a little bit of protein)

➤ Protein

- 1) Just as the acinar cells secrete some fluid, the duct cells secrete some proteins.
- 2) The main pancreatic duct contains both duct cells as well as many goblet cells.
- 3) Goblet cells in the pancreas as well as in other parts of the GI tract secrete large molecular weight glycoproteins called mucins.
- 4) The glycoproteins produced in the duct cells are synthesized and secreted on a continuous basis in small cytoplasmic vesicles.
- 5) Secretion stimulates the synthesis and thereby the secretion of the duct cell glycoprotein.

➤ NaHCO_3

- Pancreatic duct cells secrete a fluid rich in HCO_3^- (acinar cells secrete a fluid rich in NaCl).
- 1) The duct cells contain a variety of electrolyte transporters which facilitate secretion of water and electrolytes to activate existing transporters as well as to synthesis new transporters.
- 2) The pancreatic duct cells secrete NaCl , HCO_3^- and water
- 3) Secretin and Ach are the major regulators of pancreatic bicarbonate secretion from the duct.
- 4) The release of secretin from the duodenal S cells causes the pancreatic duct cells to secrete alkaline fluid (water plus HCO_3^-) by way of
 - a membrane $\text{Cl}^-/\text{HCO}_3^-$ exchanger
 - the Cl^- channels CFTR (cystic fibrosis transmembrane regulator)
 - ORCC (outward rectifying chloride channel).

➤ HCO_3^-

- Secretion of HCO_3^-

- There are a series of sequential steps leading to the secretion of NaHCO_3 by the pancreatic duct cell:

CLINICAL PHYSIOLOGICAL CORRELATION

Background: The pancreatic duct cells secrete NaHCO_3 and water. The apical (luminal) membrane contains a $\text{HCO}_3^-/\text{Cl}^-$ exchanger, CFTR (cystic fibrosis transmembrane regulator), and ORCO (outward rectifying Cl^- channel). The basolateral membrane contains $\text{Na}^+/\text{K}^+\text{ATPase}$, $\text{Na}^+/\text{HCO}_3^-$ cotransporter, Na^+/H^+ exchanger (NHE), and K^+ channels.

Problem: With these membrane components, draw a diagram which depicts the steps in the pancreatic ductular cell secretion of NaHCO_3 and water.

- 1) CO_2 and H_2O diffuse across basal membrane (BM) of the pancreatic duct cell.
- 2) HCO_3^- and Na^+ are co-transported across the BM by the $\text{Na}^+ / \text{HCO}_3^-$ cotransporter.
- 3) CO_2 plus H_2O are converted by cytoplasmic carbonic anhydrase (CA) into HCO_3^- and H^+ .
- 4) The intracellular HCO_3^- is pumped out of the cell across the apical membrane (AM) by the $\text{Cl}^- / \text{HCO}_3^-$ exchanger.
- 5) Na^+ enters the cell by the BM Na^+ / H^+ exchanger (NHE).
- Na^+ also enters the cell by the BM $\text{Na}^+ / \text{HCO}_3^-$ cotransporter.
- 6) This intracellular Na^+ exits the duct cell across the BM Na^+ / K^+ ATPase.
- Na^+ entering the cell by the BM $\text{Na}^+ - \text{HCO}_3^-$ cotransporter also exits by way of the BM $\text{Na}^+ - \text{K}^+$ pump.
- Fluid secretion by the acinar cells requires the $\text{Na}^+ - \text{K}^+$ pump to drive the $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporter in the BM.
- The $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporter moves Cl^- into the cell along with Na^+ and K^+ .

- The cytosol now contains increased K^+ from the BM Na^+-K^+ pump and from the BM $Na^+/K^+/Cl^-$ cotransporter.
- The BM Na^+-K^+ pump moves 3 Na^+ molecules out of the cell for every 2 K^+ molecules which enter.
- This imbalance of Na^+ over K^+ creates a gradient of Na^+ across the BM (higher Na^+ in the interstitial space and lower Na^+ in the cytosol of the acinar cell).
- 7) The K^+ which was initially pumped across the BM and into the cytosol by $Na^+-K^+-ATPase$ is extruded back into the interstitial space through the BM K^+ channel.
- Fluid secretion also requires the K^+ channel in the BM as well as the Cl^- channel in the AM.
- 8) Water and Na^+ flow passively cross the intercellular junctions in response to the osmotic gradient produced by the secreted Cl^- , forming the alkaline fluid (high $NaHCO_3$) in the lumen of the duct.
- 9) This lumen-negative charge drives Na^+ across the tight junctions (TJ) between the acinar cells.
- Water moves with Na^+ from the interstitial space across the TJs and into the lumen of the acinus.
- Water also moves through aquaporin channels in the BM and the AM.
- 10) Cl^- in the cytoplasm is pumped across the AM and into the lumen of the duct by CFTR (the cystic fibrosis transmembrane regulator), and by
- 11) ORCC (rectifying chloride [Cl^-] channel)
- The lumen-negative voltage pulls Na^+ into the interstitial space and Na^+ plus H_2O cross the tight junctions (TJ) and into the lumen of the duct.
- While the HCO_3^- in the ductular fluid results from the Cl^- / HCO_3^- exchanger, it is the Cl^- movement in the duct cell which causes the BM to depolarize.
- The electrical gradient across AM caused by this depolarization results in the HCO_3^-/Cl^- exchange and production of $NaHCO_3$.
- Thus, it is the opening of the CFTR Cl^- channels which exit of Cl^- cause

the HCO_3^- secretion ($\text{Cl}^- / \text{HCO}_3^-$ exchanger) and thereby the formation of NaHCO_3 in the lumen of the duct.

- Stimulation of secretion of NaHCO_3 from duct cells
- 12) Acetylcholine (Ach) acts on the BM M3 receptor
- The CCK and Ach receptors cause the intracellular concentration of Ca^{+2} ($[\text{Ca}^{+2}]_i$) to rise.
- Ach – activates Gq; Gq stimulates PLC, and PLC release DAG (diacylglycerol)
- 13) DAG stimulates PKC and IP3 .
- IP3 release stores of Ca^{+2} in the cytosol, increasing the intracellular concentration of Ca^{+2} ($[\text{Ca}^{+2}]_i$). Because Ach acts on the M3 receptor to activate PKC, but because PKC is a much less potent secretagogue as compared to PKA, secretion is a much more potent stimulus for HCO_3^- secretion.
- Ach has a lesser role in the stimulation of HCO_3^- secretion by activating Gq, which stimulates PLC.
- The increased intracellular Ca^{+2} stimulates protein kinases, which, open the K^+ channels in the BM and the Cl^- channels in the apical membrane.
- 14) Protein kinases also open the Cl^- channels in the AM, and Cl^- passes into the lumen of the intercalated ducts.
- The movements of the Cl^- into the lumen makes the lumen more negative in charge, as compared with the interstitial space.
- Secretin acts on its receptor on the BM, and the level of cAMP in the cytosol increases.
- There are PKA and PKC phosphorylation sites on CFTR.
- PKC stimulates PKA on CFTR Cl^- transporter.
- Secretin activates the cAMP signaling pathway and opens the CFTR Cl^- channels through phosphorylation.

- The secretion of Cl^- by opening the AM CFTR and Cl^- channel provides the Cl^- to exchange with the AM $\text{Cl}^- / \text{HCO}_3^-$ exchanger, and result in the Ach driving secretion of NaHCO_3 containing fluid.
- 15) Mixture of secretions from acinar and duct cells.
- The acinar cells secrete a NaCl -rich fluid, and pancreatic duct cells secrete a fluid rich in HCO_3^- .
- When the acinar and ductular cells secrete during the cephalic, gastric and intestinal phases of pancreatic secretion, these NaCl and HCO_3^- rich fluids mix.
- Because the duct cells produce much more fluid than do the acinar cells (ratio of 3:1), as the rate of secretion of pancreatic juice increases ($>0.6 \text{ mL/min}$), the concentration of HCO_3^- in the mixed fluid rises, whereas that of the Cl^- falls.
- This alkalinity of the pancreatic secretion prevents activation of the digestive acinar cell proenzymes until they leave the pancreatic duct and enter into the duodenal lumen.

CLINICAL PHYSIOLOGICAL CHALLENGE – Tests of Pancreatic Function

Case: A 45 year old alcoholic man complains of weight loss despite continued intake of food. Pancreatic insufficiency is suspected.

Question: Give the principles behind the secretin test of pancreatic function (administration of exogenous secretion and measurement of duodenal concentration of HCO_3^-), and the Lundt test meal ingestion of a standard mixed meal, and measurement of digestive enzyme activity in duodenal fluid.

Pancreatic Stones

- The pancreas secretes GP₂, which binds to the inner membrane of the zymogen granule, and aids the trafficking of these membranes back to the Golgi, to take up enzymes and to again from zymogen granules.
- Under certain pathological conditions, GP2 combines with lithostatin (the pancreatitis-associated protein, which is secreted in pancreatic juice).
- The GP2 – lithostatin complex forms protein plugs in the pancreatic duct lumen.
- These GP2-lithostatin plugs begin the process of ductular obstruction and the development of pancreatitis.
- Lithostatin may also have a bacteriostatic function that partially counters the infectious and inflammatory adverse effects of the ductal protein plugs of GP2 and lithostatin.
- Review the many mechanisms that protect the acinar cells from autodigestion by its own proteases (lysosomal enzyme, autophagosomes, zymogen granules, zymogen granule pancreatic trypsin inhibitor and other digestive enzymes, and by dilution of pancreatic juice and reduction of concentration in the intestinal lumen of active pancreatic digestive enzymes).

CLINICAL PHYSIOLOGICAL CHALLENGE – Test the Pancreas

Case: A 45 year-old alcoholic with recurrent episodes of acute pancreatitis develops weight loss and diarrhea. Pancreatic insufficiency is suspected, and the attending physician wishes to test the pancreatic function in this man.

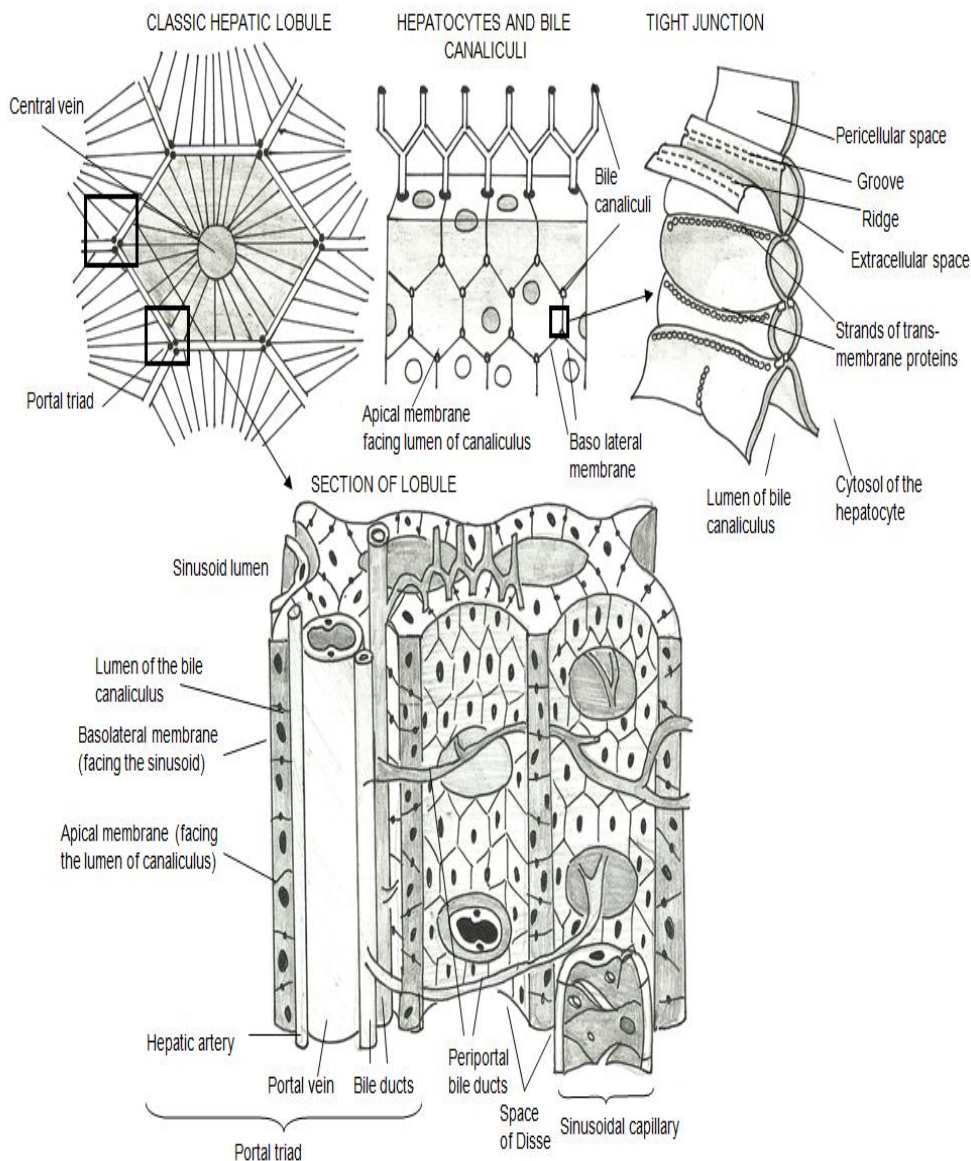
Question:

- Outline the process of normal pancreatic fluid secretion, and thereby explain the principle of the secretin test for pancreatic HCO_3^- secretion
- Describe the process of normal pancreatic secretion of enzymes and proenzymes, and thereby explain the principle of the Lundh test meal for pancreatic enzyme secretion
- Give the mechanisms by which the pancreas prevents autodigestion, including the normal post-prandial process of inhibition of the cephalic, gastric and intestinal phases of pancreatic secretion.

HEPATOBIILIARY SYSTEM

Heptatocytes, Sinusoids, and the Intrahepatic Bile System

HEPATOCYTES, SINUSOIDS, AND THE INTRAHEPATIC BILE SYSTEM



Elee

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-1, page 981.

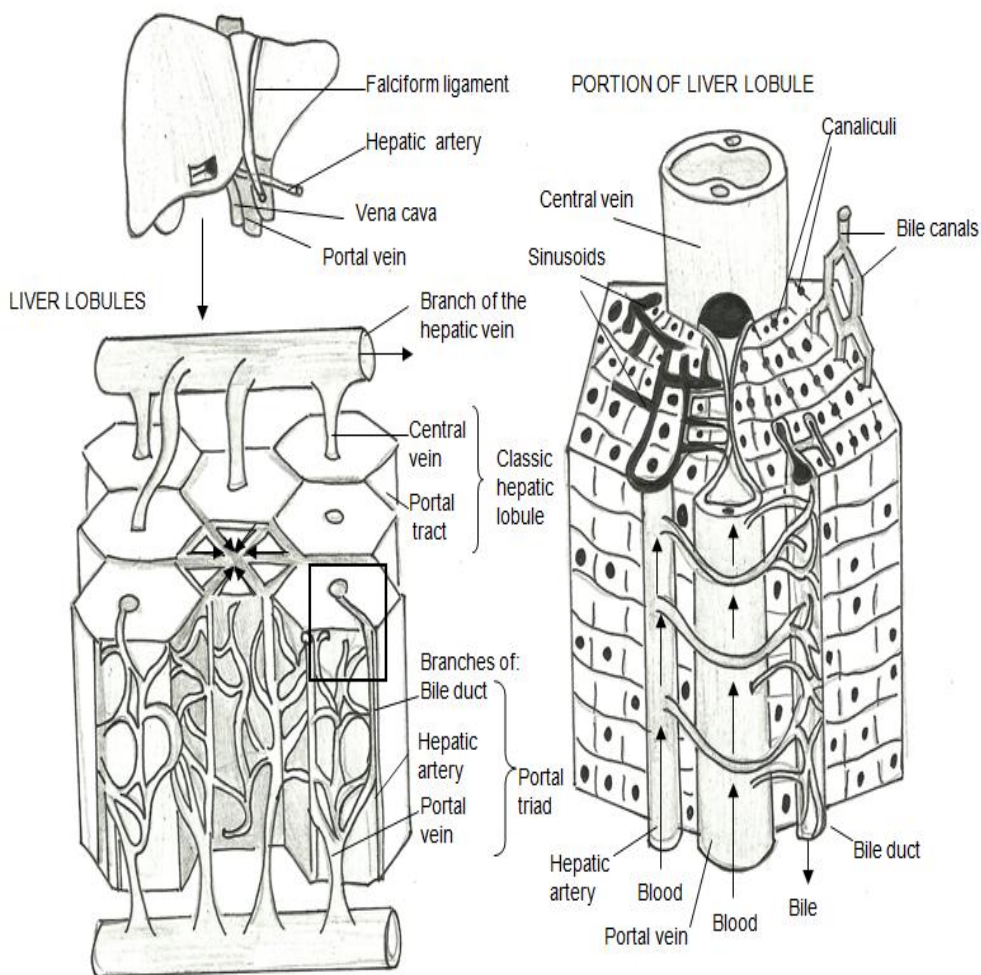
Structure

➤ Triad

- The apical membrane of the hepatocytes faces the lumen of the bile canaliculae.
- Gap junctions allow some leakyness of the membrane, and thereby some passive movement of solutes.
- The extracellular matrix in the sinusoidal spaces of Disse contains the support structure or scaffolding for the liver lobules.
- Kupffer cells (fixed monocytes in the reticuloendothelial system [RES]) are in the sinusoidal spaces (of Disse), where they are in direct contact with the sinusoidal endothelial cells and portal blood.
- Stellate (fat-storing or “Ito”) cells also are in the space of Disse.
- These Ito or stellate cells store fat, and also act both as myofibroblasts, and as the source of the fibrotic reaction which leads to cirrhosis.
- The hepatic triad is formed by the hepatic artery (HA), the portal vein (PV), and the bile duct.
- At each corner of the hexagonal hepatic lobule is a triad, and in the center is a central vein (CV).
- The portal lobule represents the hepatocytes which drain into a bile duct in the hepatic triad.
- Plasma in the sinusoidal space comes into direct contact with hepatocytes in the space of Disse.
- The endothelial cells are fenestrated and lack a basement membrane. Thus, these endothelial cells are highly permeable.
- Stellate cells are between the endothelial cells and the hepatocytes, where they are in direct contact.
- Two adjacent hepatocytes form a canaliculus, with the cells joined by tight junctions and the communicating gap junctions.

- The canalicular domain of the plasma membrane of two adjacent hepatocytes encloses and forms the bile canaliculus.

Blood Supply and Flow to the Liver



Elee

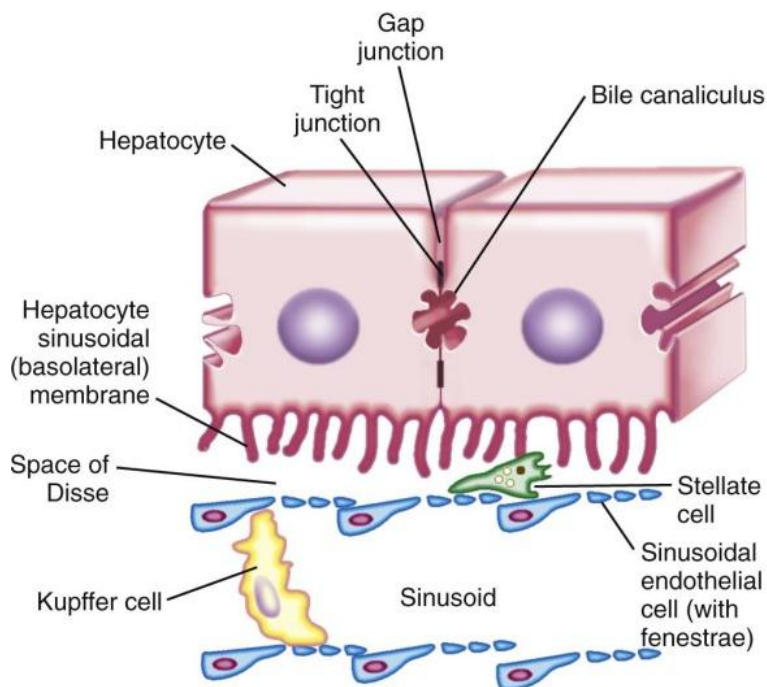
Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-2, page 983.

Blood Flow

- Blood to the liver flows in the portal vein (PV) and the hepatic artery (HA) (75% and 25%, respectively).
- Blood from the PV mixes with blood from the HA, flows to the central vein (CV), and then to the hepatic vein (HV).
- Blood from the HA flows into the sinusoidal capillaries, through the space of Disse (perisinusoidal space), between the microvilli of the hepatocyte basolateral membrane facing the sinusoid, and then into the hexagonally-shaped hepatocytes.
- Hepatocytes which are close to the terminal portal vein (PV) and the terminal hepatic arteriole in the portal triad (zone I) have the richest blood supply.
- There is heterogeneity of hepatic function in zone I and III
- Zone I hepatocytes in the portal acinae are relatively resistant to toxic damage.
- The type and amount of substrate or xenobiotic presented to zone I hepatocytes is different from zone III.
- Zone I hepatocytes specialize in oxidative metabolism, whereas zone III hepatocytes specialize in biotransformations and drug detoxification.
- Hepatocytes in zone III near the central vein (CV) have a comparatively poor blood supply, and are more vulnerable to damage.
- The sinusoidal lumen is lined by fenestrated sinusoidal endothelial cells that allow the transport of macromolecules out of the space of Disse.
- Quiescent hepatic stellate cells reside within this space of Disse, adjacent to hepatocytes and endothelial cells.
- In cirrhosis, a number of changes occur in the hepatic microcirculation, including loss of fenestrae in endothelial cells (defenestration), constriction of sinusoids, and activation of hepatic stellate cells.

- Activation of the stellate cells stimulates the formation of fibrosis.

FUNCTIONAL RELATIONSHIPS

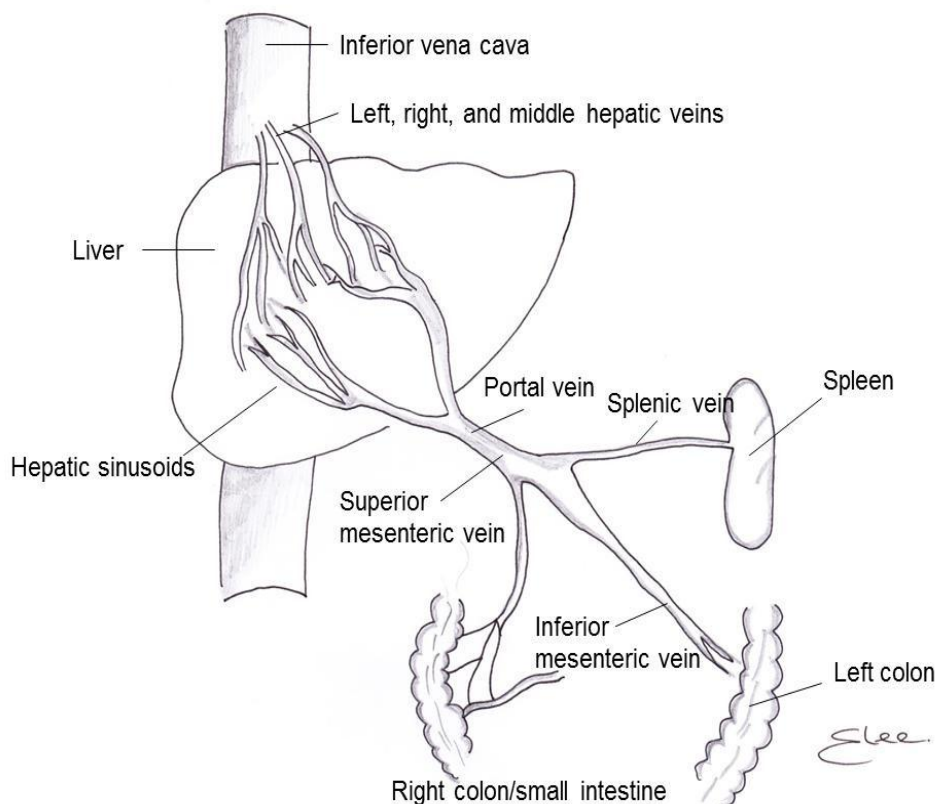


Adapted from: *Sliesinger and Fordtran's Gastrointestinal and Liver Disease*, Figure 72-1, page 1208, Ninth Edition, 2010.

- The portal circulation is important for
 - The delivery to the liver of nutrients and other substances absorbed into or secreted by the intestine.
 - The development of increased pressure in the portal circulation leads to PHT (portal hypertension), which is associated with the development of serious conditions such as bleeding esophageal varices, ascites, renal dysfunction, and hepatic encephalopathy.
 - Blood vessels that constitute the portal circulation and hepatic outflow tracts become distended as a result of increased blood flow and/or increased resistance, causing portal hypertension.

- Progressive branching division into the right and left branches of the intrahepatic portal vein and its distribution to the lobes of the liver.

ANATOMY OF THE PORTAL CIRCULATION



Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 90-1, page 1490, Ninth Edition, 2010; and *Sherlock and Dooley*, Figure 10.1, page 147, 11th Edition, 2002

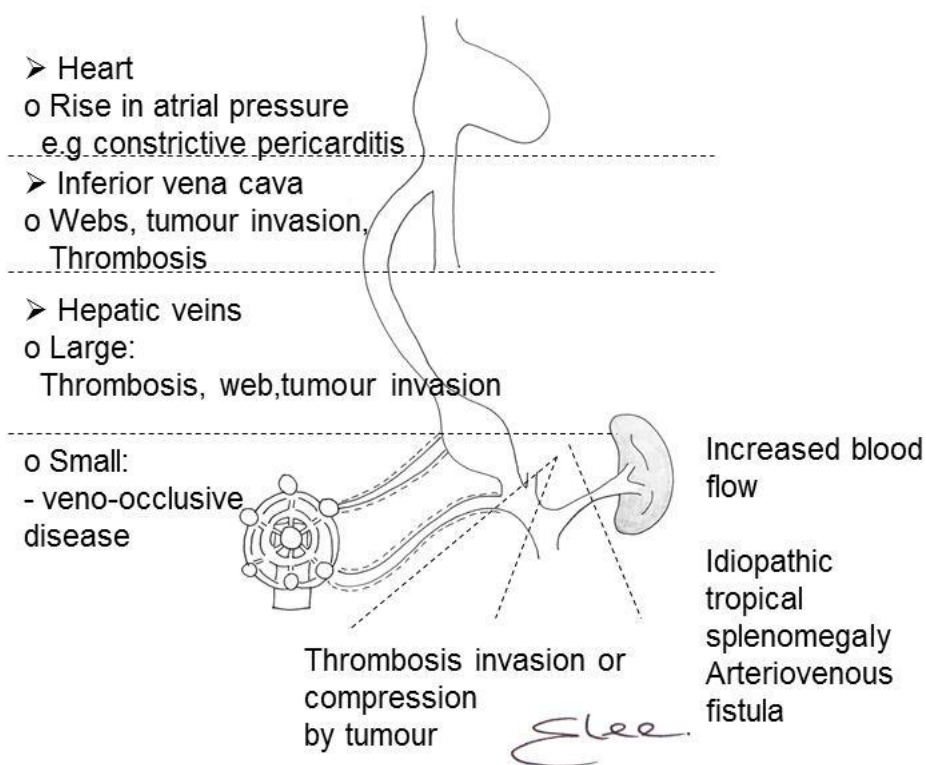
- Portal vein is posterior to the pancreas
- Division of the right branch into the anterior and posterior branches divide superiorly and inferiorly.
- Division of left branch into lateral and medial branches.

- Flows and pressures in hepatic vein (HV), portal vein (PV) and hepatic artery (HA):

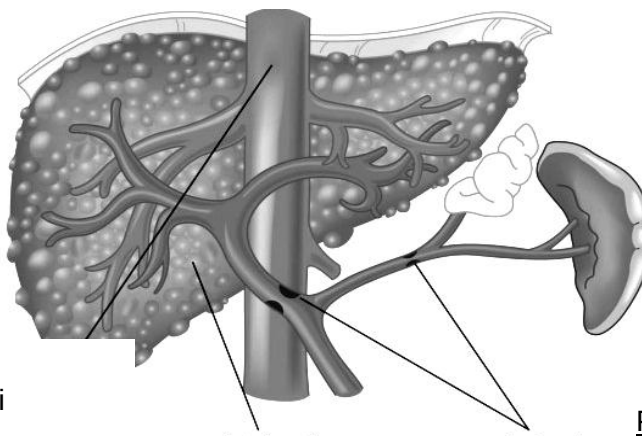
	Flow, ml/min	Pressure, mm Hg
HV	1600	4
PV	1200	7
HA	400	100

- Four segments of liver are supplied by the right anterior and posterior and the left lateral and medial branches

Causes of Portal Hypertension



CLASSIFICATION OF CAUSES OF PORTAL HYPERTENSION



Increased Blood Flow

- Arteriovenous fistula
- Idiopathic tropical splenomegaly

Post hepatic

- Budd-Chiari syndrome
- Constrictive pericarditis
- Inferior vena caval obstruction
- Right-sided heart failure
 - Webs
 - Tumour
 - Invasion
 - thrombosis
- Severe tricuspid regurgitation

Intrahepatic

- Presinusoidal (non-cirrhotic)
 - Idiopathic portal hypertension
 - Primary biliary cirrhosis
 - Sarcoidosis
 - Schistosomiasis
 - Chronic active hepatitis
 - Congenital hepatic fibrosis
 - Toxins: vinyl chloride arsenic, copper
 - Idiopathic portal hypertension
- Sinusoidal
 - Alcoholic cirrhosis
 - Alcoholic hepatitis
 - Cryptogenic cirrhosis
 - Postnecrotic cirrhosis
- Postsinusoidal
 - Sinusoidal obstruction syndrome
 - Veno-occlusive disease
 - Central hyaline sclerosis (alcoholic liver disease)

Prehepatic

- Portal vein (PV) thrombosis
- Splenic vein (SV) thrombosis
- Wedge hepatic vein pressure may be high in patients with "pre sinusoidal" causes, especially as the disease progresses, indicating

- The different sites of increased resistance to portal flow (posthepatic, intrahepatic, and prehepatic) and associated diseases are shown.
- Many diseases cause a mixed pattern.
- Portal hypertension rarely can occur exclusively as a result of increased portal flow, as occurs with arteriovenous shunts.

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 90-5, page 1493, 2010; and *Sherlock and Dooley*, Figure 10.36, page 166, 10.40, and 10.41, pages 168-169, 11th Edition 2002.

Portal Circulation

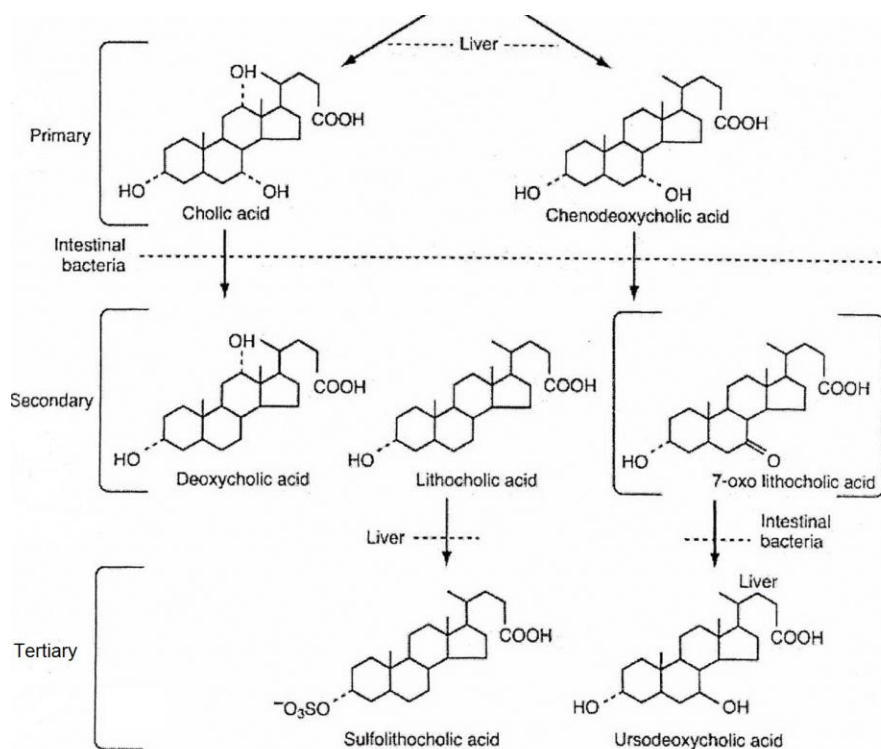
CLINICAL PHYSIOLOGICAL CHALLENGE- Portal Hypertension

Case: A 45 year old man develops esophageal varices. He consumes over 20 ounces of alcohol a day, and is suspected to having portal hypertension (PHT) from cirrhosis.

Question: Describe the portal circulation, define PHT, and explain the mechanism of development of PHT in prehepatic, intrahepatic and posthepatic disorders.

The Enterohepatic Circulation (EHC) of Bile Acids

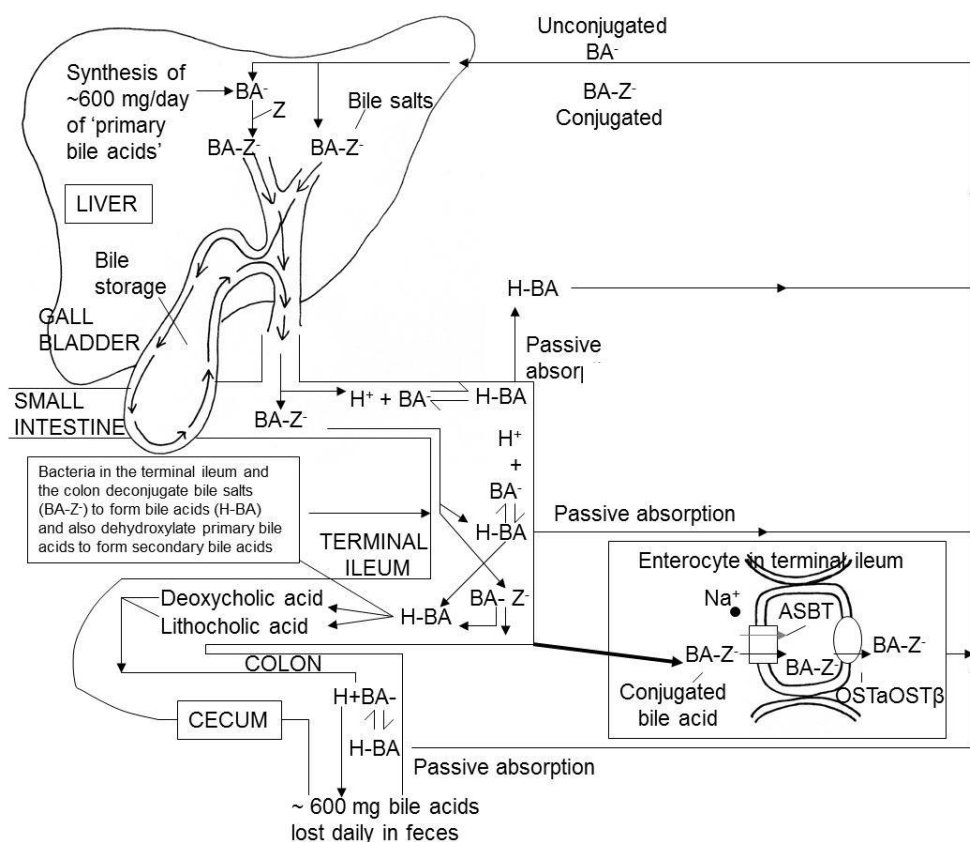
STRUCTURE OF PRIMARY, SECONDARY AND TERTIARY BILE ACIDS



Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 64-2, page 1077, Ninth Edition, 2010; and *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-9, page 995.

- To understand the enterohepatic circulation (EHC) of bile acids, one has to appreciate the role of hepatocytes, cholangiocytes, gallbladder, small intestine (especially the terminal ileum) and colon (especially the colonic bacterial).
- Bile is comprised of bile acids, bilirubin, lipids (e.g., cholesterol, phospholipids), as well as electrolytes and water
- The enterohepatic circulation (EHC) of bile requires the meal-stimulated contraction of the gallbladder, the peristalsis moving bile acids along the length of the small intestine for the absorption of lipids, bile acids uptake and exit from the ileocyte of bile acids, the role of the ileum in the regulation of hepatic synthesis of bile acids, the uptake, synthesis and excretion of the bile from the hepatocytes.

OVERVIEW OF ENTEROHEPATIC CIRCULATION OF BILE ACIDS



Elee

Printed with permission: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-13, page 999 (adapted).

➤ Liver

- The liver has 3 steps to contribute to the EHC of bile: synthesis, secretion across the canalicular membrane (aka apical membrane [AM]), and absorption across the sinusoidal membrane (SM) and back into the hepatocyte.

First, the vocabulary

➤ SM (sinusoidal membrane)

- NTC, sodium (Na^+) taurocholate cotransport polypeptide
- Na^+/K^+ ATPase
- OATP, OATP1B1 / OATP3, organic anion-transporting polypeptides
- OCT1, organic cation transport

➤ CM (canalicular membrane)

- BSEP, bile salt export pump
- MDRs, ATP-dependent phospholipid transporter (flippase)
- MDR1, ATP-dependent transporter of organic cations
- MOAT, multispecific organic anion transporter
- NPC1L1, Niemann-Pick C1 Like 1 protein
- CC, Cl^- channels
- AE2, anion exchanger isoform 2 $\text{Cl}^-/\text{HCO}_3^-$ exchanger

Synthesis

- About 600 mg per day of the primary bile acids (cholic and chenodeoxycholic acids) are synthesized in the liver each day from cholesterol.
- The daily hepatic secretion of primary bile acids (BA) is balanced by the daily loss of a similar amount of bile acids in the stools.
- The rate limiting enzyme for the hepatic synthesis of bile acids (BA) from cholesterol is 7α -hydroxylase.
- The nature of the control of 7α -hydroxylase by the ileocyte FXR /RXR and bile acid concentration will be considered a little later.

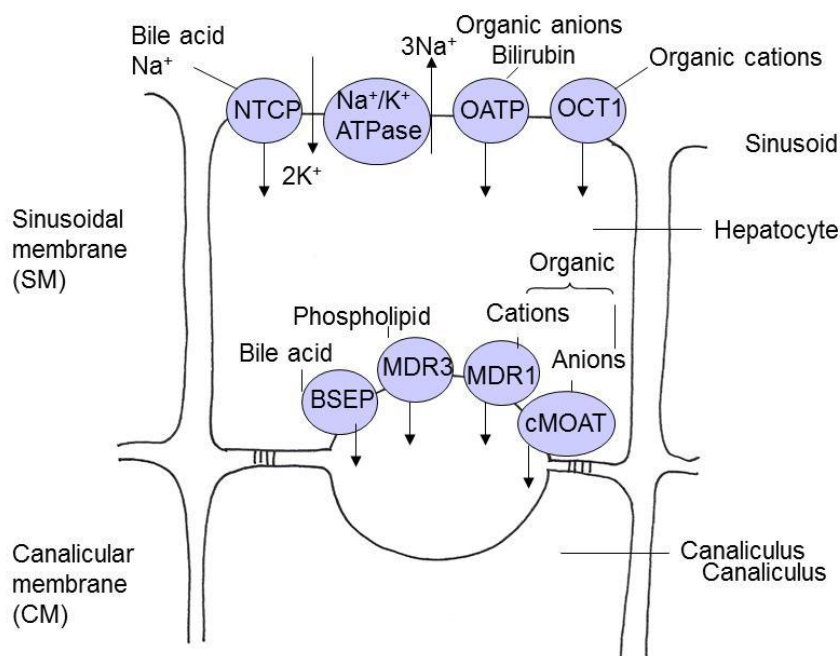
- Bile acids (BA) are conjugated mostly with the amino acids glycine and taurine (BA-Z), as well as being conjugated to sulfate or gluconate (BA-Y).
- Thus, bile acids (BA) are either protonated (H-BA) or neutral (deprotonated, BA^-) at the pHs normally seen in the lumen of the small intestine.
- To use the correct terms, H-BA or BA (neutral) are protonated or neutral bile acids, and BA^- (deprotonated H-BA) are bile salts (BS), as also are BA-Z and BA-Y.
- Because BA-Z and BA-Y are negatively charged, they are also bile salts.
- In the hepatic cytoplasm, BA-Z are attached to binding proteins which are also transported by NTCP (BP: dihydrodiol dehydrogenase, glutathione-S-transferase B, and hepatic fatty acid binding protein).
- BA-2 – binding proteins move by a vesicular pathway towards the AM (apical membrane, aka CM, canalicular membrane).
- AM actively secrete bile acids and bile salts (bile salt dependent and independent pathways), bile pigments (eg, bilirubin), electrolytes and water (active secretion plus diffusion), as well as vesicular transport of cholesterol, phospholipids and IgA protein into the bile canaliculi.
- There are numerous bile acid efflux transporters in the AM.
- There are also numerous aquaporin isoforms in the AM.

CLINICAL PHYSIOLOGICAL CHALLENGE: The Role of Liver in the Enterohepatic Circulation of Bile Acids

Case: A 50 year old women with proven primary biliary cirrhosis (PBC) develops pruritis.

Question: Describe the process of the hepatocyte sinusoidal uptake, synthesis, and canalicular secretion of the bile acids (steps in the enterohepatic circulation of bile acids).

HEPATOCTYTE BILE ACID TRANSPORTERS IN THE SINUSOIDAL MEMBRANES (SM) AND CANALICULAR MEMBRANES (CM)



Abbreviations: BSEP, bile salt export pump; cMOAT, multispecific organic ion transporter; NTCP, Na^+ -taurocholate cotransporting polypeptide; OATP, organic cation transporter; NHE, Na^+/H^+ exchanger.

- **Hepatic Canalicular Membrane (CM) Secretion (Transport) of Bile Acids and Salts into Canaliculus and Ductules**
 - The CM transports unconjugated bile salts, protonated bile acids H^+ -BA, conjugated bile salts (BA-Z-[Z= glycine or taurine]), as well as BA- $[\text{HCO}_3^-]$ and SO_4^{2-} , HCO_3^- , and Cl^- .
 - The CM: BSEP, the bile salt export pump; cMOAT, the multispecific organic anion transporter; MDR1, the ATP-dependent transporter of organic cations; and MDR3, an ATP-dependent phospholipid transporter (flippase); and a HCO_3^- transporter.
 - Transport of BA- out of the hepatocyte and across the CM is mediated by BSEP (bile salt export pump), a member (ABCB11) of the ABC (ATP-binding cassette) protein family.

- The affinity of BSEP for the negatively charged bile salts is $TC > TUDCA > GC$.
- The bile salts BA-Y (bile acids conjugated to sulfate or gluconate) are transported by ATP-dependant MRP2.
- The concentration of bile salts (BA- and BA-Z) is higher in the canalicular cells as compared to the hepatocytes.
- Other compounds in the hepatocytes are secreted in a vectorial fashion across the CM and into the bile canaliculus.

Exchange transporters	Co-transporters	Channels
➤ Na^+-K^+	$Na^+-HCO_3^-$	Cl^-
➤ Na^+-AA	GLUT2	K^-
➤ Na^+-H^+		
➤ H^+-Ca^{+2}		

➤ Sinusoidal Membrane (SM) Absorption

- At the Na^+ - taurocholate cotransporting polypeptide (NTCP; gene symbols SLC 10A1) mediates the uptake of BA-Z and BA-, as well as neutral sterols and cyclic oligopeptides.
- NTCP carries some drugs such as the diuretic furosemide, and the calcium channel blocker verapamil.
- NTCP carries half of the unconjugated bile acids, and the other half enter by passive diffusion.
- Sodium-dependent uptake of bile acids through NTCP is driven by an inwardly directed sodium gradient generated by Na^+ , K^+ - ATPase, and the membrane potential is generated in part by a K^+ channel.
- The SM also contains a Na^+-H^+ exchanger and a $Na^+-HCO_3^-$ cotransporter (symporter).
- In the SM are also organic anion transporting polypeptides, OCT1 (organic cation transport 1), and NHE (Na^+ / H^+ exchanger).

- The Na^+ - independent bile acid uptake is mediated by the organic anion-transporting polypeptides OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3).
 - ↓ ASBT in the ileal AM, decreasing bile acid absorption into the ileocytes.
 - ↑ BSEP, so ↑ BA is transported out of the ileocytes.
 - ↓ NTCP, thereby decreasing the uptake of conjugated (BA-Z) and unconjugated bile salts (BA) into the hepatocytes across the CM.
- Exit of bile acids into systemic circulation
- ASBT (apical sodium - dependent bile acid transporter, SLC10A2) of conjugated bile acids absorption by cholangiocytes of the larger bile ducts.
 - Cholangiocytes also express FIC1 (ATP8B1), a P-type ATPase mutated in progressive familial intrahepatic cholestasis.
 - The canalicular membrane also expresses ATP-dependent export pumps that transports phospholipid (multidrug resistance protein 3, MDR3; ABCB4), cholesterol and plant steroids (ABCG5/BCG8), and drug metabolites (MDR1; ABCB1) into bile.
 - Bile acids may then exit across the basolateral membrane of the hepatocyte and into the hepatic arterial circulation via either the heteromeric transporter OST α – OST β or an ATP –dependent carrier, MRP3 (ABCC3).
 - The CM chloride channels, and the Cl^- and HCO_3^- anion exchanger isoform 2 (AE2) secretes bicarbonate.
 - In the hepatocyte cytosole, the macromolecules may be degraded by cytosomal lysosomes or the macromolecules be transported cross the hepatocytes and across the canalicular membrane by exocytosis, may be transported by exocytosis.

Role of the gallbladder in the EHC of Bile Acids (BA)

- The Na^+ - H^+ exchanger and the HCO_3^- - Cl^- exchanger in the apical membrane of the gallbladder epithelium lead to the absorption of NaCl.

- Because of this, gallbladder absorption of water from the bile increases the concentration of bile acids, cholesterol (Chol), phospholipids (PL) and organic anions and cations.
- If the concentration of bile acids, Chol and PL are normal, the lipids in gallbladder bile remain soluble.
- When this process is deranged, cholesterol gallstones may form.
- The development and complications of gallstone is considered in a later section.

Role of Small Intestine in the EHC of BA

➤ Duodenum and Jejunum

- Only small amounts of BAs are absorbed by passive diffusion along the length of the small intestine.
- The bile passes through the extrahepatic biliary tree, after about half of the hepatic bile has become concentrated by water absorption in the gallbladder.
- This mixture of hepatic and gallbladder bile enters the duodenum, where the bile acids solubilize lipids and continue the process of lipid absorption.
- The concentration of BAs which is required to form the micelle is known as the “critical micellar concentration” (CMC).
- The enterohepatic circulation of bile salts (EHC) functions to maintain the CMC in the lumen of the proximal intestine, and thereby facilitate the absorption of lipids.
- Only small amounts of bile acid are absorbed by diffusion in the jejunum.
- Non-ionic diffusion of the protonated unconjugated bile acids (H - BA) is much higher than is ionic (BA⁻)diffusion.
- This low absorption of bile provides the means to continue to have sufficient bile acids in the lumen to solubilize and to facilitate the absorption of about 95% exogenous and endogenous lipids.

- The complex and integrated process of lipid absorption is considered in a later section; here we only briefly consider lipid absorption against the overall perspective of understanding the enterohepatic circulation of bile acids.
- Once the concentration of bile in the duodenal lumen reaches a critical concentration (about 5 mM), the bile acid monomers form micelles.
- This critical concentration of bile acids is called the “critical micellar concentration” (CMC).
- When the CMC is reached, the negatively charged spheres (“micelles”) are formed.
- These simple micelles solubilize the lipid digestive products in the intestinal lumen (fatty acids, B-glycerol, phospholipids, free cholesterol).
- These micelles that have solubilized the lipid digestive products are called mixed micelles (MM).
- MM diffuse across the unstirred water layer on the luminal side of the enterocyte brush border (apical) membrane (AM).
- In the aqueous phase in the intestinal lumen, the water-soluble lipids, glycerol, as well as short- and medium- chain length fatty acids diffuse across the AM, through the cytosol of the enterocyte, and across the BM into the portal circulation
- Some of the lipids solubilized in the MM partition into the AM, and diffuse into the cytosol of the enterocyte.
- Some fatty acids are transported across the AM, by FAT.
- The EHC also provides a pathway for the secretion of cholesterol from the body, by way of the metabolism of CH to BAs.
- Cholesterol is transported across the AM by the Niemann-Pick C1 like1 protein transporter (NPC1L1).
- When the MM are depleted of their solubilized lipids, the now simple micelles move back into intestinal lumen where they solubilize more lipids, and once again shuttle across the UWL and AM.

➤ Intestinal Lumen

- The content of bacteria in the intestinal lumen increases from the proximal to the distal small intestine (10^4 to $\sim 10^7$ per hpf [high power field]).
- Bacteria in the terminal ileum and colon deconjugate bile salts (BA-Z) to form bile acids (H-BA).
- Bacteria also dehydroxylate the primary bile acids secreted by liver (cholic and chenich acids, forming the secondary bile acids deoxycholic and lithcholic, respectively.
- The secondary bile acids may be dehydroxylated again by intestinal bacteria into the tertiary bile acids.
- The tertiary bile acids may be absorbed and enter the enterohepatocyte circulation together with the primary and secondary bile acids.
- In the terminal ileum and colon, bacteria deconjugate a small amount of these bile salts to form unconjugated bile acids ($H \cdot BA \leftrightarrow H^+ + BA^-$), thereby allowing $H \cdot BA$.
- This deconjugation by luminal bacteria allows the conjugated bile acids ($H \cdot BA$) to be passively absorbed by non-ionic diffusion.
- Secondary metabolism of bile acids by the intestinal bacteria microbiotica includes
 - 7α -dehydroxylation
 - Deconjugation
 - Epimerization of 3α - and 7α - hydroxyl groups
 - Hepatic reduction of the 7-oxo derivative of chenodeoxycholic acid to 7-oxo lithocolic acid
 - Hepatic re-epimerization of 3β -hydroxy bile acids
 - Sulfation at the 3 or 7 positions by the liver and kidney
- Like the unconjugated primary bile acids, the unconjugated secondary bile acids are absorbed in the ileum, pass in the portal blood to the hepatocyte sinusoidal membrane, where they are taken up by the hepatocytes.and reconstituted in the hepatocyte cytosol.

➤ Ileum

- Once the lipids have been absorbed, the bile acids pass along the length of the jejunum to the ileum.
- The bile salts (BA-Z) are efficiently reabsorbed by ASBT, then active uptake by ileal ASBT (Na⁺/bile transporter) is low.
- Conjugated bile acids are actively transported across the ileocyte AM as conjugated bile acids (BA-Z) by ASBT (apical sodium bile acid transporter; (gene symbol, SLC10A2).
- Bile acids in the cytosol of the ileocytes are actively transported across the BM by BSEP (bile salt export protein; gene symbol ABC B11).
- The unconjugated primary, secondary and tertiary bile acids are also cycled in the portal circulation back to the liver.
- The bile acids which are not absorbed by the small intestine pass into the colon.
- The usual loss of unabsorbed bile acids in the feces (about 600 mg per day) is matched by hepatic synthesis of bile acids.
- The BAs which are taken by the hepatocyte sinusoidal membrane (SM) mix with any newly synthesized BAs.
- The BAs traffic to the canalicular membrane (CM) of the hepatocyte where they are transported into the bile ducts back into the duodenal lumen, to form BAMs.

Role of the Hepatocyte Sinusoidal Membrane (SM)

- These bile acids return to the liver through the portal blood, and are taken up by the sinusoidal membrane (SM) of the hepatocyte.
- The bile acids cycle in the EHC (liver-intestine and back to the liver) numerous times (4 to 6) with each meal.

- Because the intestinal absorption of bile acids is so high, the EHC is very efficient, and the liver does not need to produce large amounts of bile acids each day.
- Transcriptional regulator of the nuclear bile acid receptor:
 - 1° BA are synthesized by the hepatocytes
 - 1° BA increase FXR in the ileocytes
 - FGF 19 passes to the liver in the portal venous blood.
 - FGF 19 interacts with the dimeric receptor FGFR4/β-klotho present on the SM of the hepatocyte.
 - The activated FGFR4/β-klotho receptor initiates a phosphorylation cascade.
 - This phosphorylation cascade causes transcriptional repression of the gene which encodes cholesterol 7α-hydroxylase, the rate-limiting enzyme in bile acid biosynthesis.
 - ↓ hepatic cholesterol 7α-hydroxylase, ↓ 1° BA are synthesized in the hepatocytes.
- Hepatic sinusoidal membrane (SM)
 - ↓ ASBT in the ileal AM, decreasing bile acid absorption into the ileocytes.
 - ↑ BSEP, so ↑ BA is transported out of the ileocytes.
 - ↓ NTCP, thereby decreasing the uptake of conjugated (BA-Z) and unconjugated bile salts (BA) into the hepatocytes across the CM.

Secretion of HCO₃⁻ and water by Cholangiocytes

- Cholangiocytes express a variety of transporters:

AM	PM
○ CFTR	○ Na ⁺ / HCO ₃ ⁻ cotransporter
○ Non-CFTR Cl ⁻ channels	○ NHE (Na ⁺ / H ⁺ exchanger)
○ AE2 Cl ⁻ / HCO ₃ ⁻ exchanger	○ K ⁺ channel
○ ASBT absorption of Na ⁺ /	

BA⁻

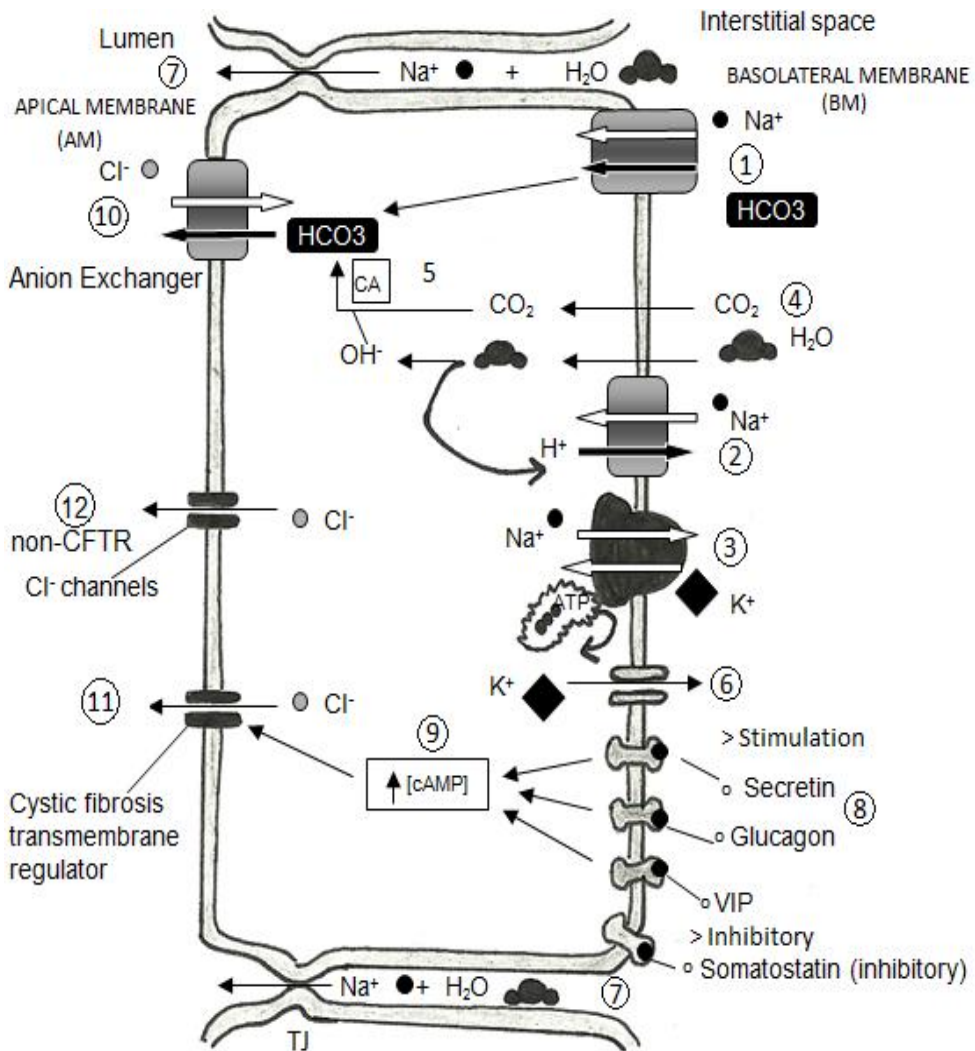
- SGLT1 (SLC5A, sodium-glucose cotransporter)
- Numerous aquaporin isoforms

○ IRP3 / OST tra

Salt and water

- 1) Na⁺ enters the cholangiocyte with HCO₃⁻ across the BM by the way of Na⁺ / HCO₃⁻ cotransporter.
- The intrahepatic and extrahepatic bile duct cholangiocyte epithelial cells secrete HCO₃⁻ and water.
- 2) Na⁺ also crosses the cholangiocyte BM with NHE, the Na⁺ / H⁺ exchanger.
- 3) The BM Na⁺ / K⁺ ATPase maintains low intracellular [Na⁺] and high [K⁺].
- The H⁺ / Ca²⁺ exchanger maintains low intracellular [Ca²⁺].
- 4) H₂O and CO₂ diffuse across the BM.
- 5) In the cytosol of the cholangiocyte, carbonic anhydrase (CA) forms HCO₃⁻ and H⁺
- Intracellular H⁺ formed from CO₂ and H₂O by CA leaves the cholangiocytes across the BM by NHE.
- Na⁺ which has entered the cholangiocyte through BM Na⁺ / HCO₃⁻ cotransporter exits the cell across BM Na⁺ / K⁺ ATPase.
- 6) K⁺ which entered the cholangiocyte across BM Na⁺ / K⁺ ATPase leaves the cell through K⁺ channel in the BM.

SECRETION OF HCO_3^- AND WATER BY CHOLANGIOCYTES



Abbreviations: CA, carbonic anhydrase; CFTR, cystic fibrosis transmembrane regulator; TJ, tight junction

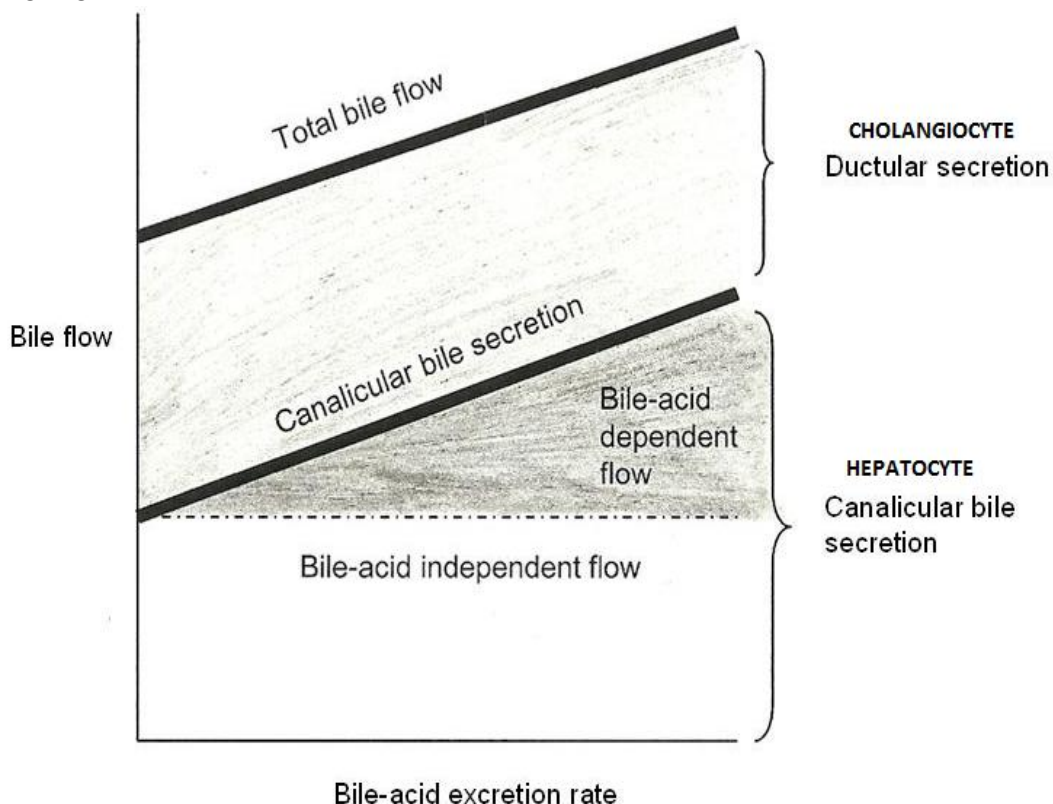
Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 46-11, page 996.

- 7) Na^+ and H_2O cross the tight junctions (TJs) between the cholangiocytes and into the lumen.
- 8) Secretin, glucagon and VIP increase cAMP in the cytosol, whereas somatostatin decreases cAMP levels.
- $\uparrow$ cAMP enhances the secretion of bile (a choleretic effect).
- 9) Under basal conditions, AQP8 (aquaporin 8) is in intracellular vesicles. In the presence of cAMP, AQP8 inserts into the canalicular membrane.
- AQP8 acts as a water channel, increasing water permeability across (transcellular movement of water).
- 10) HCO_3^- which crossed the BM with Na^+ by way of the $\text{Na}^+ / \text{HCO}_3^-$ AE2 (anion exchanger aka $\text{Cl}^- / \text{HCO}_3^-$ exchanger).
- 11) cAMP opens CFTR with Cl^- leaving the cholangiocyte.
- 12) Some Cl^- also leaves the cell through non-CFTR channels.

CLINICAL PHYSIOLOGICAL CORRELATION – Cholangiocyte Function

Background: The cholangiocyte sinusoidal membrane (SM) contains the AE2 (anion exchanger, aka $\text{HCO}_3^-/\text{Cl}^-$ exchanger, as well as CFTR and non-CFTR Cl^- channels. The cholangiocyte basolateral membrane (BM) contains the Na^+/K^+ ATPase, Na^+/H^+ exchanger (NHE), and the NaHCO_3 transporter.

Problem: With these membrane components, draw a diagram which depicts the steps in the cholangiocyte secretion of NaHCO_3 and water.

Bile Flow

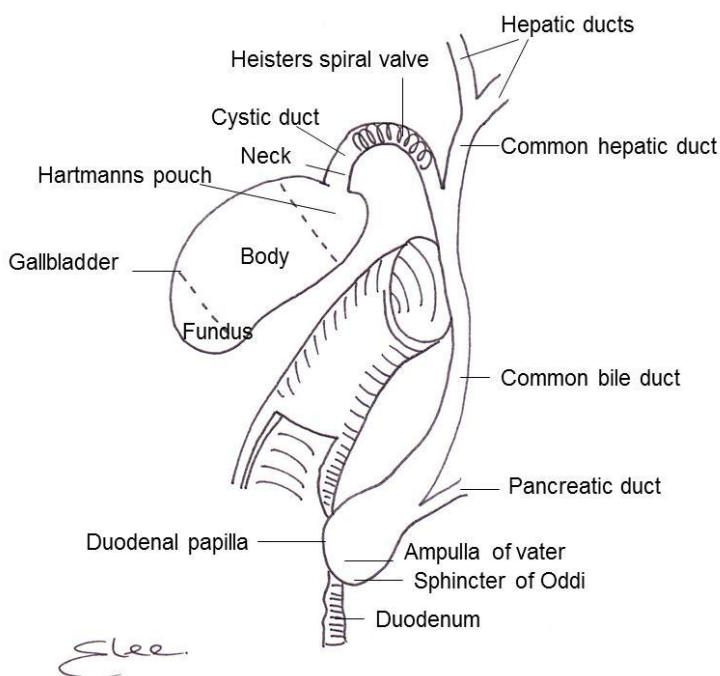
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- Bile is made up of hepatocyte canalicular and cholangiocyte ductular secretion.
- Canalicular secretion is comprised of bile acid-independent flow (from the secretion of organic compounds) as well as bile acid-dependent flow.
- As the rate of bile acid excretion is enhanced, bile acid-dependent flow rises, and the total flow from those three components rises.
- Note that when there is no excretion of bile acids (bile-acid excretion rate is zero), there is still flow of bile containing water and electrolytes (bile acid independent flow).
- As the rate of bile acid excretion increases, hepatic bile-acid dependent flow increases, so canalicular bile secretion rises.
- As the rate of bile acid excretion increases cholangiocyte ductular secretion also rises.

- The composition of bile is also modified by the absorption of water in the gallbladder, concentrating 20-fold the hepatic bile.
- Hepatic bile flows down the common hepatic duct (CHD).
- About half of the hepatic bile continues down the CHD into the common bile duct (CBD) through the sphincter of Oddi, and into the lumen of the duodenum.
- The other half of the hepatic bile is diverted from the common hepatic duct (CHD) into the cystic duct, and then into the gallbladder.

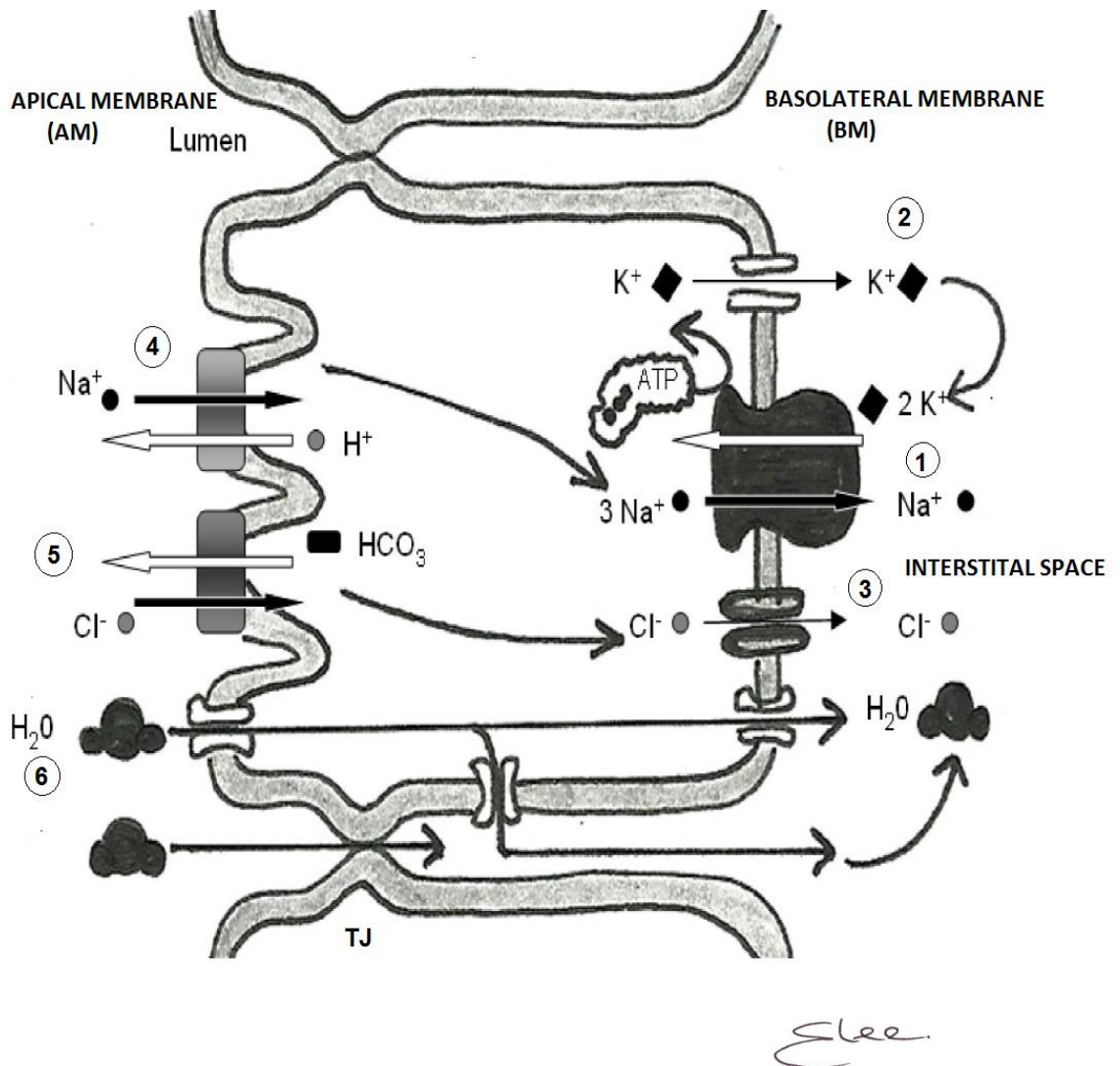
Gallbladder

ANATOMY OF HEPATOBILIARY TREE AND GALLBLADDER



Adapted from: Sherlock and Dooley, Figure 1.6, page 3, 11th Edition, 2002

FLUID REABSORPTION BY THE GALLBLADDER EPITHELIUM



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009, Figure 46-12, page 997.

CLINICAL PHYSIOLOGICAL CORRELATION – Gallbladder Absorption

Background: The basolateral membrane (BM) of the gallbladder epithelium $\text{Na}^+/\text{K}^+\text{ATPase}$, as well as K^+ , Cl^- and H_2O channels. The apical membrane (AM) contains both Na^+/H^+ exchanger (NHE) and $\text{HCO}_3^-/\text{Cl}^-$ exchanger, as well as H_2O channels.

Problem: With these membrane components, draw a diagram which depicts the absorption of H_2O by the gallbladder epithelium.

Absorption of Electrolytes and Water by Gallbladder

- The gallbladder concentrates gallbladder bile from dilute hepatic bile
 - 1) Cl^- is taken up by the apical $\text{Cl}^- / \text{HCO}_3^-$ exchanger of the gallbladder epithelium.
 - 2) This Cl^- leaves the gallbladder epithelial cell through the BM Cl^- channel.
 - 3) The BM ATP-dependant $\text{Na}^+ - \text{K}^+$ pump in the BM provides a Na^+ gradient.
 - 4) K^+ transported into the gallbladder epithelial cell across the BM exits the cell through the BM K^+ channel.
 - 5) The NHE (Na^+ / H^+ exchanger) in the AM secretes H^+ from the cell, and absorbs Na^+ from the hepatic bile.
 - 6) H_2O flows across the tight junctions (TJ) between the epithelial cells in the gallbladder.
 - 7) H_2O also flows through pores in the AM and BM, removing H_2O from the hepatic bile and from the more concentrated gallbladder bile.
 - Because the exchange of Na^+ and H^+ is greater than for HCO_3^- and Cl^- , the gallbladder bile becomes more acidic than the hepatic bile.
 - This acidity of gallbladder bile enhances the solubility of bile acids in the more concentrated gallbladder bile.

Pathophysiology of Gallstone Formation

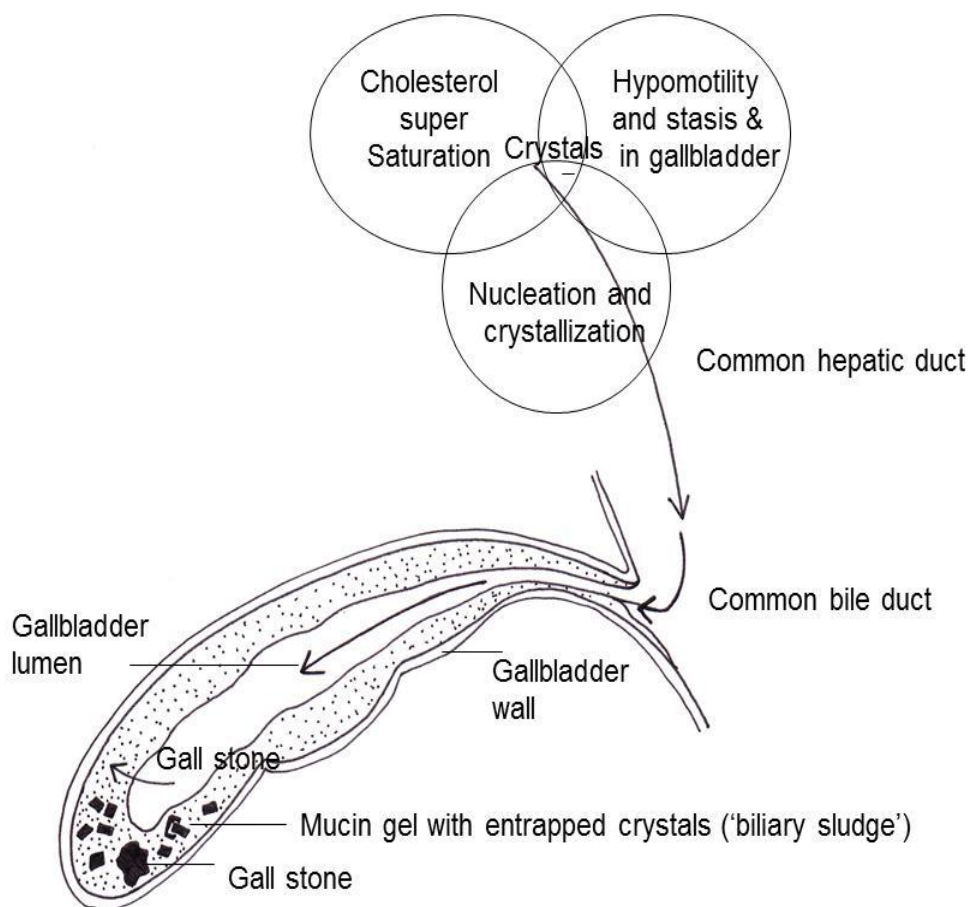
- Gallstones are usually formed from cholesterol, bilirubin, or a mixture of the two.
- Cholesterol
 - The steps leading to bilirubin gallstones will be covered in the next section on bilirubin metabolism.
 - The steps involved in the hepatobiliary aspects of cholesterol metabolism is also covered in a later section.
 - If the concentrations of bile acids, cholesterol, phospholipids or bilirubin are abnormal in the bile, the lipids may be insoluble.
 - The bile becomes “lithogenic”; lipid becomes insoluble in bile, and gallstones are formed.
 - Conditions required for cholesterol stones to form, may be too much cholesterol in the bile, or too little solubilize the cholesterol.

CLINICAL PHYSIOLOGICAL CORRELATION – Cholesterol Gallstones

Case: Interruption of the enterohepatic secretion, increased hepatic secretion of cholesterol, or decreased synthesis of bile acids, or impaired gallbladder motility may result in the formation of cholesterol gallstones. These may cause blockage of the cystic duct and cholecystitis blockage of the common bile duct and jaundice as well as cholangitis, and blockage of the pancreatic duct causing acute pancreatitis.

Question: Describe the pathophysiology of the formation of cholesterol gallstones

Formation of Cholesterol Gallstones

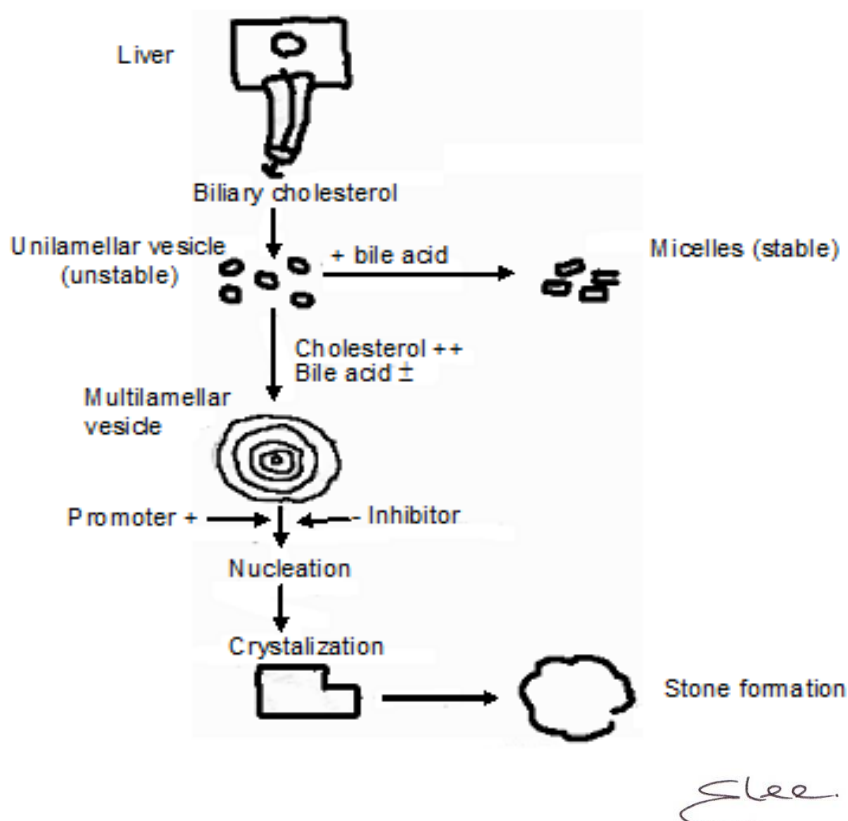


- When bile does not reach the intestine because there is for example an obstruction of bile from a gallstone in the common bile duct, no bilirubin reaches the colon, no urobilinogen or strobilin are formed, and the stools become pale in colour and the urine becomes dark (tea-coloured).

Adapted from: *Slisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 55-1, page 1069, Ninth Edition, 2010

- Overview of formation of cholesterol gallstone
 - Cholesterol supersaturation ($\uparrow$ cholesterol or $\downarrow$ bile acid hepatic synthesis)
 - Stasis of bile in gallbladder (from stasis)
 - $\uparrow$ secretion of mucin gell in gallbladder
 - Formation of mucin glycoprotein complexes
 - Formation of cholesterol crystals around the mucin glycoprotein complexes (nidation)
- When the bile is supersaturated with cholesterol, unstable unilamellar vesicles form.
- Multilamellar vesicles then form from the unstable unilamellar vesicles.
- In the presence of nidation factors, nucleation and crystalization occurs, and over time gallstone form.
- In normal persons, gallbladder bile may become supersaturated with cholesterol for a short interval during fasting.

Development of Lithogenic Bile



Adapted from Sherlock and Dooley, Figure 34.4, page 599, 11th Edition, 2002

- Cholesterol gallstone disease is a liver disorders arising from lithogenic bile.

Cholesterol metabolism

- Small intestine
 - Digestion
 - Absorption
 - Enterocyte metabolism
 - Enterocyte secretion
- Liver
 - Sinusoidal uptake
 - Synthesis and secretion

- Role of the liver in the control of cholesterol homeostasis
 - HMG-CoA reductase controls the rate of synthesis of cholesterol in the hepatocytes.
 - Cholesterol is also taken up across the hepatocyte sinusoidal membrane, mixed with synthesized hepatic cholesterol, and exits the hepatocyte across the canalicular membrane and into the ductules, as part of the EHC.
 - The major means of eliminating cholesterol from the body is by their conversion to bile acids, acting through the activity of 7 α -hydroxylase.
 - Other routes of elimination of small amounts of cholesterol from the body includes
 - Synthesis of steroid hormones
 - Sloughing of skin and intestinal epithelial cells
 - Loss in the bile
 - Loss in the feces.
- Intestinal digestion and uptake of cholesterol
 - Dietary and secretory cholesterol are in the ester form, and the free cholesterol must just be de-esterified to free cholesterol by pancreatic cholesterol ester hydrolase (CEH).
 - The free cholesterol is solubilized in bile salt micelles with TAGs and PLs (phospholipids); forming mixed micelles.
 - The mixed micelles diffuse across the intestinal water layer (IWL), and up close to the BBM (brush border membrane) of the enterocyte).
 - The lipid constituents partition from the mixed micelle and cross the apical membrane (AM) of the enterocytes, by passive diffusion through the lipid bilayer of the AM, as well as by transport proteins in the AM transporter for cholesterol is NPC1L1 (the Niemann – Pick C1 like transporter protein).

➤ Enterocyte cytosole

- Once the free cholesterol is in the enterocyte, it is esterified by ACAT (acyl CoA ester cholesterol transferase), in the endoplasmic reticulum.
- Esterified cholesterol is solubilized by binding to apoprotein.
- The enterocytes synthesize apoprotein I and II (A-I and A-II).
- A-I and A-II are part of the apoproteins forming chylomicrons in the enterocyte.
- The apolipoproteins pass to Golgi apparatus, where they are glycosylated.
- In the enterocyte, and more so in the hepatocyte, cholesterol is synthesized.
- The chylomicrons remnants in the fed state and VLDLs pass through large interendothelial channels of lymphatic capillaries, and enter the lymph fluid in the lymphatic system.
- The ATP-binding cassette (ABC) transporter, ABCA1 translocates cholesterol, and phospholipids (PLs) to the BM.
- The cholesterol and PLs form lipid domains that interact with amphipathic α -helices in apolipoproteins.
- The enterocytes (like the liver) contain HMG-co-reductase, and also synthesize cholesterol.

➤ Small Intestinal “Secretion” of Cholesterol

- Enterocytes absorb, metabolize and export dietary (exogenous) as well as secreted (endogenous) lipids.
- Dietary triacylglycerol (TAG, aka triglycerides) and cholesterol are exported across the enterocyte basolateral membrane (BM) as chylomicrons.
- Chylomicrons are 80% to 90% TAG, plus cholesterol, phospholipids, and apoproteins are secreted by the enterocyte, passing through the BM.

- Chylomicrons pass from the BM to lymphatics, to the thoracic duct, and into the systemic circulation.
- The TAG in chylomicrons are partially broken down by lipoprotein lipase (LPL).
- LPL is present in the walls of the capillaries in muscle and adipose tissue.
- The glycerol and fatty acids are digested and leave the chylomicrons, which now contain just cholesterol.
- These cholesterol-enriched chylomicrons are called remnant chylomicrons.
- The remnant chylomicrons contain small amounts of DAG, and large amounts of cholesterol.
- The remnant chylomicrons pass in the systemic circulation to the liver.
- The digestion of VLDL by LDL yields cholesterol (and phospholipid) from the surface of the VLDLs.
- This VLDL-derived cholesterol leaves the non-hepatic tissue by the cholesterol efflux transporter (CET), ABCA1.
- This cholesterol binds to HDL (high density lipoproteins).
- This free cholesterol plus the phospholipid lecithin, are acted upon by the enzyme LCAT cholesterol acyltransferase.
- The LCAT forms cholesterol esters plus lysolecithin from the free cholesterol and lecithin.
- The HDL is now enriched with cholesterol esters (CE).
- HDL-CE binds to SR-B1 (scavenger receptor class B type 1) on the hepatocyte.
- SR-B1 leads to the uptake of HDL-CE (this is not a process of endocytosis).

- HDL-CE may also transfer its CE to VLDL, IDL and LDL.
 - This transfer of HDL-CE occurs through the action of CETP (cholesterol ester transfer protein).
 - Thus HDL removes cholesterol from peripheral tissues by
 - SR-B1, and
 - CETP
 - This removal of cholesterol from peripheral tissues by SR-B1 and CETP, and the eventual excretion of cholesterol in bile is called reverse cholesterol transport.
- Role of hepatic sinusoidal membrane in cholesterol metabolism
- The chylomicron and VLDL cross the sinusoidal membrane (SM) of the hepatocyte and mix with, the absorbed cholesterol synthesized de novo through the action of HMG CoA reductase.
 - The same steps are followed for the association with apoproteins, glycosylation of apolipoproteins, the budding off of chylomicrons and VLDL from the Golgi apparatus, and the transport of the chylomicrons across the CM of the hepatocyte and into the bile.
 - The hepatic uptake of cholesterol is mediated by three proteins: the low-density lipoprotein (LDL) receptor (LDLR) for LDL, by scavenger receptor class B type I (SR-BI) for high-density lipoprotein (HDL), and by the chylomicron remnant receptor (CMRR) for chylomicron remnants (CMR).
 - The remnant chylomicrons bind in the liver to the sinusoidal membrane (SM) receptors
 - LDL-related receptor, and
 - LDL-receptor (low-density lipoprotein)
 - Enterocytes absorb, metabolize and export dietary (exogenous) as well as secreted (endogenous) lipids.
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- The remnant chylomicrons pass in the systemic circulation to the liver.
- The remnant chylomicrons bound to the LDL- and LDL-related receptors enter the hepatocyte by receptor-mediated endocytosis.
- In the hepatocyte, lysosomes break down to remnant chylomicrons.
- The TAG broken down by LPL contains certain long-chain fatty acids (LCFA) which are taken up only by the liver.
- These LCFA cross the SM of the hepatocyte by facilitated uptake as well as “flip-flow” across the membrane.
- Cholesterol delivered to the liver in chylomicron remnants join cholesterol passing into hepatocyte in LDL.
- LDLs are the major carrier of the cholesterol in the blood.
- Blood LDLs are taken up into the hepatocytes by endocytosis.

- The liver also synthesizes cholesterol de novo from acetyl CoA and mevalonate.
- Some cholesterol is used for the synthesis of bile salts (BSs) via the “neutral” pathway.
- Some cholesterol is used for the synthesis of bile salts via the “acidic” pathway.
- The chylomicron and VLDL pass through the intestinal lymphatic, and in the portal circulation.
- The small amount of TAG delivered to the hepatocytes in the remnant chylomicrons undergoes breakdown into glycerol and fatty acids (FAs).
- The fatty acids in the liver undergo metabolism, by β -oxidation, to Acetyl CoA, or they are used to reform TAG.
- Acetyl CoA may be used for
 - Entry into the citric acid cycle to produce energy
 - Production of acetoacetate, to be used for energy not by the liver but instead by the brain, kidney, and muscle.
 - Production of ketone bodies (acetoacetate, acetone and β -hydroxybutyrate) which may accumulate in excess during fasting or diabetic ketoacidosis.
- The hepatic FAs re-esterified with glycerol to TAG are bound to lipoprotein, forming VLDL (very low density lipoprotein).
- VLDL may be stored in the liver, or exported from the liver for use by the peripheral tissue, where the VLDL are broken down by LDL.
- In the fasting state, VLDL shuttle endogenous TAG to muscle and adipose tissue, whereas chylomicrons are important in the fed state.
- The enzyme HMG-CoA reductase is in the membrane of the ER (endoplasmic reticulum) of the hepatocyte.
- The activity of HMG-CoA reductase is increased by
 - ↓ cell cholesterol
 - ↓ cell mevalonate

- ↑ cell demand for metabolites derived from mevalonate
- ↑ gene translation
- Depletion of the bile acid pool
- This upregulation occurs by the process of
 - ↑ stability HMG-CoA reductase.
- The activity of HMG-CoA reductase is reduced by fasting, high levels of cholesterol in cells, and sterol acting on sterol regulatory elements (SRE) and sterol regulatory element binding proteins (SREBPs).
- At the Golgi apparatus the apolipoproteins are glycosylated.
- The lipid is digested, absorbed and metabolised in the enterocyte (please see section on lipid absorption in the chapter small intestine)

CLINICAL PHYSIOLOGICAL CHALLENGE – Control of Cholesterol Metabolism

Case: A 45 year old woman with primary biliary cirrhosis (PBC) has hypercholesterolemia and xanthelasma.

Questions: Outline the role of the liver in maintaining normal concentrations of cholesterol in the blood.

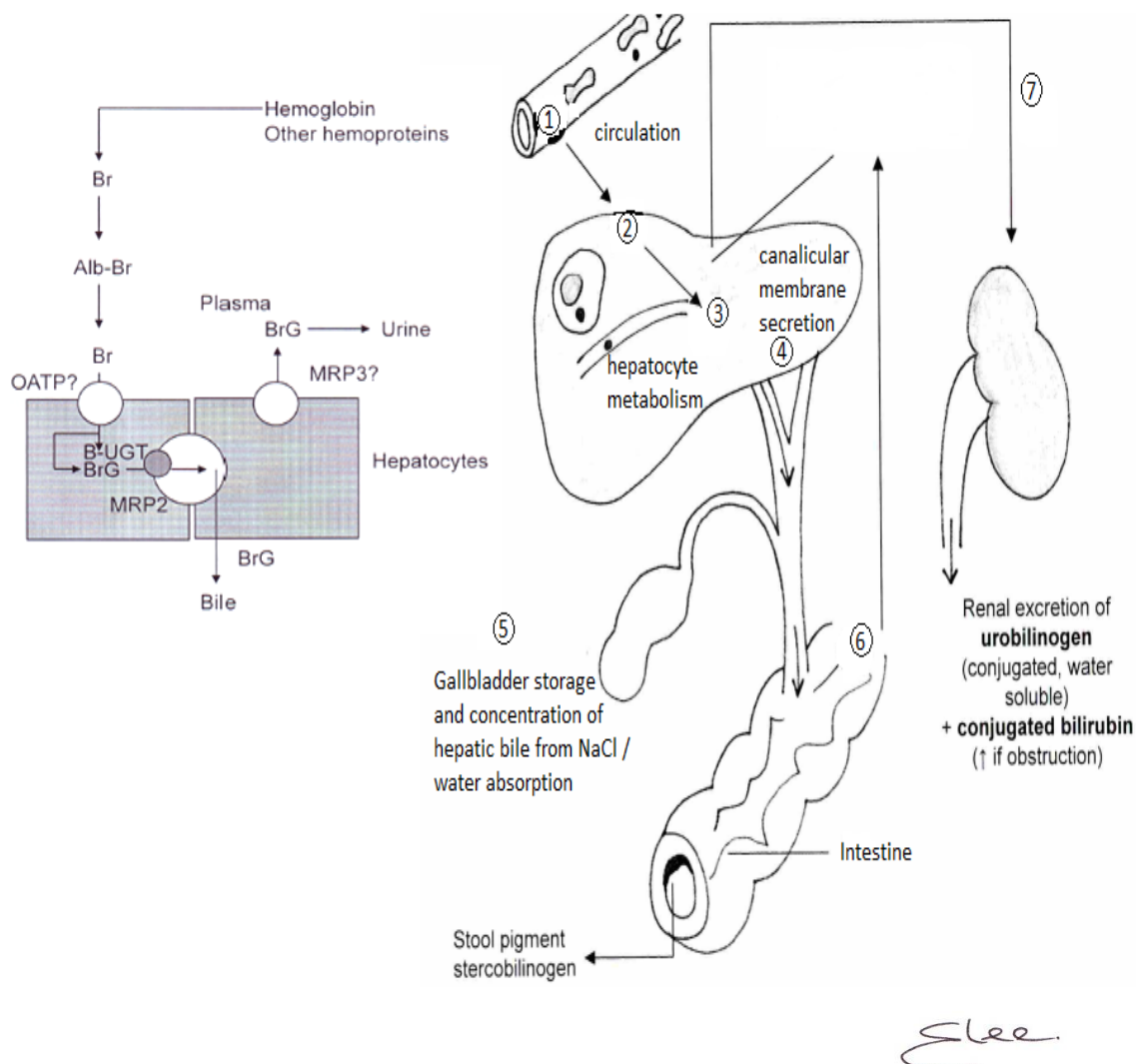
➤ Hepatic cholesterol balance

- Free cholesterol is derived from intracellular synthesis, and from the uptake of chylomicron remnants and lipoprotein from the circulation.
- Some cholesterol is stored as cholesterol ester: ACAT (acyl CoA – cholesterol ester transferase, esterifies free cholesterol to fatty acids)
- CEH (cholesteryl ester hydrolase hydrolyses the ester linkage).
- Bile acids are synthesized from free cholesterol, and both are secreted into bile.
- 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting step for the synthesis of cholesterol.

- Hepatic excretion of cholesterol across the canalicular membrane (CM)
 - The apoproteins (except for apolipoprotein [A-I] traffic to the SER, where they associate with lipid droplets.
 - Apolipoproteins solubilize cholesterol and phospholipids, and generate nascent HDL particles.
 - This interaction solubilizes the lipids and generates nascent HDL.
 - The nascent HDL particles dissociate from the cell.
 - Nascent chylomicrons and VLDLs (very low density lipoproteins) arrive at the cis face of the Golgi apparatus.
 - Some cholesterol is used for the formation of very-low-density lipoprotein (VLDL), which is secreted into the portal blood.
 - Apolipoprotein A-I is associated with chylomicrons in the Golgi apparatus.
 - The vesicles which carry chylomicrons or VLDLs bud off from the trans- Golgi apparatus, forming transparent vesicles.
 - The transport vesicles traffic to the BM, releasing their chylomicron or VLDLs by exocytosis.
 - Glycerol, short chain, and medium chain fatty acids pass through the enterocyte, across the BM, and enter blood capillary.
 - These products avoid the apolipoproteins, transport vesicles, and lymphatics.
 - The synthesis is regulated by two rate-limiting enzymes cholesterol 7 α -hydroxylase (CYP7A1), the “neutral pathway”, and sterol 27-hydroxylase (CYP27A1), the “acidic” pathways.
 - The HDL particles leave the hepatocyte.
 - Cholesterol (Chol), bile salts (BS), and phospholipids (PL) are secreted across the canalicular membrane by the three lipid transporters ABCG5/G8, ABC B11, and ABCB4, respectively.

Bilirubin metabolism

STEPS IN BILIRUBIN (Br) FORMATION, METABOLISM, AND TRANSPORT



Adapted from: Davey P. Wiley-Blackwell, 2006, Figure 22, page 46; and from *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*. Figure 20-1, Page 324, Ninth Edition, 2010.

➤ STEP 1 – Blood Circulation

- When RBCs (red blood cells) reach the end of their lifespan of approximately 120 days, these senescent cells are taken up by the macrophages in the hepatic reticuloendothelial system (RES).
- In the RES, the hemoglobin in the RBCs is broken down by heme oxygenase to biliverdin and bilirubin (Br)
- Bilirubin in the blood is bound to albumin (alb), to form alb-Br.
- There is also likely a carrier for alb-Br complex.
- In the blood, unconjugated bilirubin is conjugated to glucuronic acid in the ER.

➤ STEP 2 – Hepatocyte Sinusoidal Membrane (SM) Uptake

- Electrochemical and electrogenic processes
- A Br-Cl⁻ - exchanger, possibly, by one of the OATPs.
- Small organic cations (OC⁺) are transported by OCT1 and OCT2 in the hepatic sinusoidal membrane.
- Large organic cations are transported by OATP-A, and some enter the hepatocytes by way of the H-CA exchanger.

➤ STEP 3 – Hepatocyte Metabolism

- The Br in the cytosol of the hepatocyte is in phospholipids vesicles.
- Br in the phospholipid vesicles in the hepatocyte cytosol diffuses into the ER.
- In the presence of UETs (uridine diphosphate glucuronosyl transferases), Br is conjugated to glucuronic acid (G), forming water soluble bilirubin mono- and digluconides (BrG)
- This BrG diffuses out of the ER, across the cytosol to the MRP2 transporter in the hepatocyte canalicular membrane.

➤ STEP 4 – Hepatocyte Canalicular Membrane Secretion

- MRP2 transports most BrG across the hepatocyte apical membrane and into the bile canaliculus.
 - Some BrG crosses the membrane (possibly by MRP3), into plasma, and from the plasma into the urine
- **STEP 5 – Gallbladder Storage and Concentration of Hepatic Bile**
- Br in the hepatic bile enters the gallbladder, or trickles through the sphincter.
 - Upon the release of CCK in the upper intestine in response to fat and protein in the upper portion of the small intestine, the Br is excreted in gallbladder bile by way of the contraction of the wall of the gallbladder
- **STEP 6 – Intestinal Metabolism**
- Some of the conjugated bilirubin is deconjugated back into bilirubin in the intestinal lumen, and some conjugated bilirubin is converted by colonic bacteria to urobilinogen (brown sterobilin which gives stool its characteristic brown colour), is passed into the stools.
 - Some BrG is converted by colonic bacteria to urobilinogen.
 - Sterobilin gives stool its characteristic brown colour); the brown stool is passed from the body.
 - Some of the Brg is deconjugated back into bilirubin in the intestinal lumen.
- **STEP 7 – Renal Excretion**
- Some urobilinogen is absorbed in the small intestine, and converted to the yellow pigment urobilin, which is excreted by the kidney into the urine.
 - When bile does not reach the intestine because for example an obstruction of bile from a gallstone in the common bile duct, no bilirubin reaches the colon, no urobilinogen or strobilin are formed, and the stools become pale in colour.
- When there is increased breakdown of red blood cells, or obstruction of some parts of the hepatobiliary tree, bilirubin gallstones may form.

CLINICAL PHYSIOLOGICAL CHALLENGE – Bilirubin Gallstones

Case: A 28 year old mother of four healthy children develops RUQ pain and tenderness. Acute cholecystitis is diagnosed

Question:

- Describe the steps in the metabolism of bilirubin
- Outline the pathophysiology of the development of gallstones.
- Explain the colour of the urine and stools in persons with obstruction of the common bile duct (CBD)

CLINICAL PHYSIOLOGICAL CORRELATION – Bilirubin Metabolism

Case: A 32 year old women develops malaise, abdominal discomfort and jaundice.

Question: Draw a picture of bilirubin metabolism to distinguish between prehepatic, hepatic and posthepatic causes of jaundice.

Complications of Gallstones

The complications are similar for gallstones formed from cholesterol, bilirubin, or both chemical.

➤ Gallbladder and Cystic Duct

- Asymptomatic stones (75%)
- Stone intermittently obstructing cystic duct, causing intermittent biliary pain (20%).
- Stone impacted in cystic duct, causing acute cholecystitis (10%).
- Stone in cystic duct compressing or fistulizing into the bile, causing Mirizzi's syndrome (< 0.1%).
- Long standing cholelithiasis, resulting in gallbladder carcinoma (< 0.1%).

➤ Common Bile Duct

- Stone impacted in distal bile duct, causing jaundice, biliary type pain, and risk of ascending cholangitis or acute biliary pancreatitis (5%).

- Stone eroding through gallbladder into duodenum, resulting in cholecystoenteric fistula (prerequisite for gallstone ileus).
- Stone may erode into stomach to cause gastric outlet obstruction (Bouveret's syndrome).
- Stone impacted in cystic duct causing acute cholecystitis (10%).

Adapted from: *Slisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 65-7, page 1106, Ninth Edition, 2010.

CLINICAL PHYSIOLOGICAL CHALLENGE

Case: A 45 year old woman with primary biliary cirrhosis (PBC) has hypercholesterolemia and xanthelasma.

Questions: Outline the role of the liver in maintaining normal concentrations of cholesterol in the blood.

> Causes of Biliary obstruction

- Bilirubin from destruction of red cells circulates bound to albumin
- Hepatic conjugation into water - soluble bilirubin glucuronide, formed by glucuronyl transferase
- Excretion into bile
- Gut bacterial action → Glucuronide
- stercobilinogen → stool pigment (excreted)
- Conjugated bilirubin from gut into blood → Urobilinogen
- Urobilinogen excreted in urine

> Causes of Jaundice

- Pre-hepatic; ↑ Hemoglobin destruction (usually due to hemolysis → ↑ unconjugated bilirubin in blood)
- Hepatic disease – (e.g., viral hepatitis) interferes with bilirubin uptake; cholestasis reduces conjugation and excretion into common hepatic duct
- Post-hepatic – impaired bilirubin excretion into bile (= cholestasis)
 - Intrahepatic (drug, PBC, viruses)
 - Extrahepatic (biliary stones, cancer, pancreatic disease)

Adapted from: Davey P. Medicine at a glance. Second Edition, *Blackwell Publishing*, Figure 22, page 46, 2002

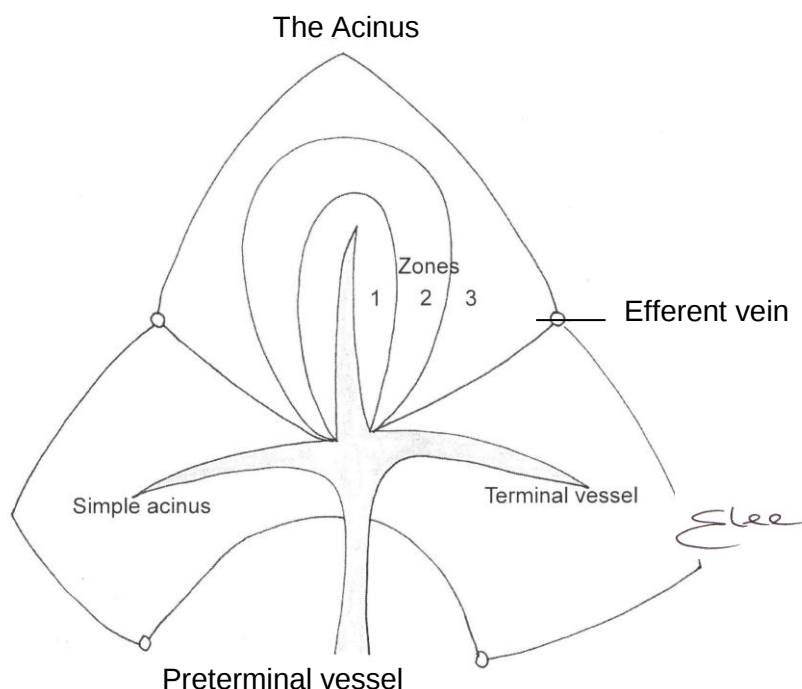
CLINICAL PHYSIOLOGICAL CHALLENGE - Gallstones

Case: A 28 year old mother of four healthy children develops RUQ pain and tenderness. Acute cholecystitis is diagnosed.

Question:

- Describe the steps in the metabolism of bilirubin
- Outline the pathophysiology of the development of gallstones.
- Explain the colour of the urine and stools in persons with obstruction of the common bile duct (CBD)

Heterogeneity of hepatocyte metabolic function in the hepatic zones



- Rappaport zone 1 is adjacent to the entry (portal venous) system
- Zone 3 is adjacent to the exit (hepatic venous) system

Adapted from: *Scientific Basis for Clinical Practice in Gastroenterology and Hepatology*, 2002, 1st Edition, Figure 1.12, page 8.

Oxidative Energy	Zone I (Oxidation)	Zone III (Ketogenesis)
➤ Amino Acids	○ Catabolism of AA	○ Glutamine Synthesis
➤ Carbohydrates	○ Gluconeogenesis ○ Glycogen degradation	○ Glycogen Synthesis ○ Glycolysis ○ Ketogenesis, glycolysis, glycogen and glutamine synthesis
➤ Lipids	○ Oxidation of FAs ○ HMG CoA reductase	○ Liponeogenesis ○ Cholesterol synthesis
➤ Bile	○ Bile acid dependent canalicular flow	○ 7 α -hydroxylase ○ Bile acid independent canalicular flow
➤ Urea	○ Ureagenesis	○ Biotransformation

Abbreviations: AA, amino acids; FA, fatty acids

Source: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Table 46-1, page 984.

- This means that toxic damage more often occurs in the vulnerable contrilobular zone III hepatocytes than in zone I. This toxic damage is also known as DILI, drug induced liver injury.
- The 150 (or more) isoforms of the cytochrome P- (CYP)450 enzyme are endoplasmic reticulum (ER) proteins.
- CYP 450 enzymes catalyze the phase I biotransformation reactions, metabolizing about half of all drugs.
- The CYP-450 mono-oxygenases insert an atom of oxygen into the substrates, rendering the substrate more water-soluble, allowing the substate to be reactive with the phase III enzymes.

- The reactions of the important CYP 3A isoform of the CYP-450 enzyme, include hydroxylation, dealkylation, and dehalogenation.
- The phase III enzymes further increase the water solubility of the substrate by conjugating the substrate to gluconate, glutathione (GSH) or sulfate (cytosolic sulfotransferases).
- Other phase III enzymes which enhance the water solubility of the substrate include the sulfotransferases and glutathione-S-transferases.
- Two nuclear receptors are present in the liver and intestine, and function as transcription factors responsible for drug metabolism.
- SXR (steroid and xenobiotic receptor) and CAR (constitutive androstane receptor) interact with xenobiotics and drugs, bind to DNA response units and thereby, alter the expression of drug metabolizing enzymes, as well as MDR1 (metabolizing resistance transporter).

Clinicopathological presentations of DILI

Phenotype	Features	Examples of causative drugs
➤ Acute fatty liver with lactic acidosis	○ Microvesicular steatosis with systemic mitochondrial dysfunction	– Valproate, fialuridine, nucleoside analogues
➤ Acute hepatic necrosis	○ Collapse and necrosis of liver parenchyma	– Many drugs, including isoniazid
➤ Acute liver failure	○ Collapse and necrosis of liver parenchyma INR > 1.5 and encephalopathy	– Many drug, including isoniazid, bromfenac, nitrofurantoin
➤ Acute viral hepatitis-like liver injury	○ Prodrome of malaise, fatigue and lassitude	– Isoniazid, halothane
➤ Autoimmune-like hepatitis	○ Detectable autoantibodies and/or autoimmune features on liver biopsy specimen	– Minocycline, nitrofurantoin, methyldopa

➤ Without inflammation	○ Pruritis with hyperbilirubinemia	– Anabolic steroids, estrogen
Phenotype	Features	Examples of causative drugs
➤ Cholestatic hepatitis	○ Elevated serum levels of alkaline phosphatase and bilirubin	– Amoxicillin-clavulanate
➤ Cirrhosis	○ Variable degrees of collagenization	– Methotrexate
➤ Immunoallergic hepatitis	○ Skin rash ○ Eosinophilia and fever (drug allergy)	– Cotrimazole, phenytoin
➤ Nodular regeneration	○ Microscopic or macroscopic liver nodules	– Azathioprine
➤ Non-alcoholic fatty liver	○ Microvesicular or macrovesicular steatosis ○ With or without ballooning and steatohepatitis	– Amiodarone, tamoxifen
➤ Sinusoidal obstruction syndrome	○ Obliteration of central veins	– Cyclophosphamide, busulfan, pyrrolizidine alkaloids
➤ Vanishing bile duct syndrome	○ Paucity of interlobular bile ducts with cholestasis	– β lactam antibiotics

Abbreviations: DILI, drug induced liver injury; INR, international normalized ratio

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Possible risk factors involved in the pathogenesis of DILI

➤ Drug	➤ Environment	➤ Host
○ Class	○ Diet	○ Age
○ Dose	○ Toxins	○ Sex
○ Duration	○ Exposure to tobacco	○ Weight
○ Drug-drug interactions	○ Alcohol	○ Genetic factors
	○ Coffee	○ Metabolism
	○ Chemicals	○ Immune factors
	○ Pollutant	○ Other disease
	○ Oxidants	
	○ Probiotics	
➤ Drug		
○ Drug factors have not been clearly associated with liver injury in pre-clinical toxicology test systems or in patients with DILI.		
○ Drug-drug interactions could alter the concentration of a drug or a reactive metabolite at a cellular location involved in the initiation, maintenance or concentration of resolution of liver injury.		
○ DILI is difficult to exclude when multiple drugs or herbal products are co-administered		
➤ Environment		
○ The microenvironment and macroenvironment are known to vary greatly within and among individuals but are difficult to study and quantify.		
○ Metabolomic approaches and studies of the human microbiome may provide important insights into the role of environment factors in the pathogenesis of DILI.		

➤ Host

- Genome-wide association studies have demonstrated reproducible associations between several host genetic polymorphisms and DILI, but in general host factors have only rarely been implicated in the pathogenesis of DILI

Abbreviation: DILI, drug induced liver injury

Adapted from: Tujlos S and Fontana RJ. *Nat. Rev Gastroenterol Hepatol* 2011;8:202-211

Useful Background: Factors to consider in the diagnosis of DILI

➤ Time to onset

- Variable range but usually < 12 months

➤ Clinical features at presentation

- Can be asymptomatic
- Rash and eosinophilia are found infrequently
- Classification into hepatocellular versus mixed/and or cholestatic liver injury on the basis of R value

$R = (\text{initial ALT/ULN}) / (\text{AP/ULN})$: patient with an R value > 5 have hepatocellular liver injury, and $R < 2$ is indicative of cholestatic liver injury.

The R value helps the clinician to identify other etiologies of acute liver injury to consider and exclude (i.e. differential diagnosis)

➤ Risk factors for hepatotoxicity

- Few clinical risk factors established with certainty
- Possible risk factors involved in the pathogenesis of DILI have been proposed

➤ Course of liver injury following drug cessation

- Drug withdrawal (dechallenge) is problematic in patients with fulminant liver failure and those who develop chronic injury

- Exclusion of competing causes of liver injury
 - Laboratory and radiological testing for hepatitis A, hepatitis B, hepatitis C, alcohol, autoimmune disorders and pancreaticobiliary diseases
- Prior reports of hepatotoxicity
 - Problematic with newly approved drugs and herbal products
 - Currently no centralised source of information
- Drug rechallenge
 - Rarely done and gives variable results
- Liver histology
 - DILI can mimic nearly all known forms of acute and chronic liver injury

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; DILI, drug induced liver injury; ULN, upper limit of normal

Acetaminophen hepatotoxicity as a common example of DILI

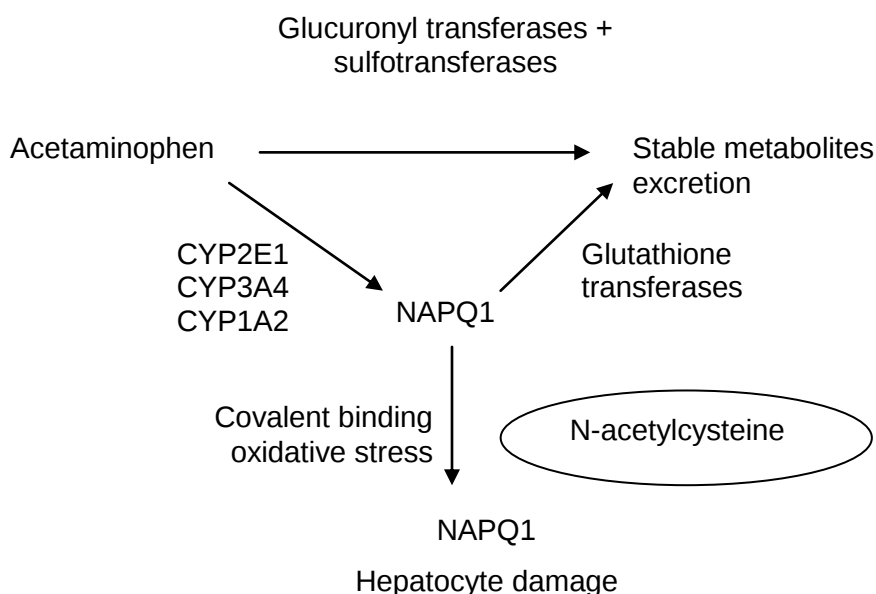
- Role of host metabolic system
 - Most of ingested acetaminophen is usually transformed by glucuronyl transferases and sulfotransferases to stable metabolites.
 - These stable metabolites of the ingested acetaminophen are excreted into the urine and bile.
 - If this usual system is overwhelmed, a larger proportion of acetaminophen is oxidatively metabolized by CYP isoenzymes to the highly reactive intermediate metabolite, NAPQ1.
 - NAPQ1 covalently binds to hepatocyte proteins and can disrupt mitochondrial function, resulting in hepatocyte damage.
 - Administration of N-acetylcysteine restores the depleted stores of hepatic glutathione and reduces cellular damage.

CLINICAL PHYSIOLOGICAL CHALLENGE – Drug-induced Liver Injury

Case: An 18 year-old distraught first year medical student consumes 10 grams of acetaminophen plus 250 ml of vodka over a two hour interval. S(he) is brought to the ER when mental confusion was noted.

Question:

- What are the possible drug, environment and host factors involved in the pathogenesis of DILI (drug-induced liver injury)?
- Give the role of the metabolic and host immune systems in the pathogenesis of acetaminophen hepatotoxicity



➤ Role of host immune system

- Normal circumstances – common variant of MHC II
- The release of MMP9 from infiltrating macrophages facilitates liver regeneration via its binding to CD44 receptors on lymphocytes.
- The MHC susceptible variant is usually a minor polymorphism.
- By itself this polymorphism does not account for all of intraindividual variation in DILI susceptibility, and the generally low incidence of DILI caused by a particular drug.

- Drug are small molecules that may become bound by proteins (hapttenized), forming drug-protein complexes during physiological circumstances or following metabolic activation *in vivo*.
- Usually, drug and protein form a drug – protein complex.
- The drug-protein complexes are phagocytosed by APCs (antigen presenting cells).
- The APCs present the drug or drug-protein/peptide complexes to Helper T-cells, by way of common variant of MHC II.
- Common MHC II s resistant to the formation of hepatocyte damage.
- Macrophages infiltrating the liver recognize damaged hepatocytes, and release proinflammatory cytokine (IL-1 β , TNF), as well as proregenerative cytokines (IL-10, IL-6).
- No hepatocyte damage, no DILI – because of common MHC II.
- Susceptibility – susceptible variant of MHC II.
- Differences in human leukocyte antigen genotypes can lead to variation in MHC peptide-binding grooves.
- ↓ expression of MMP4 causes ↓ CD44 binding on lymphocytes, less regeneration and more inflammation and hepatic damage.

Abbreviations: APC, antigen presenting cell; drug induced liver injury; MHC, major histocompatibility complex

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CLINICAL PHYSIOLOGICAL CHALLENGE – Drug-induced Liver Injury

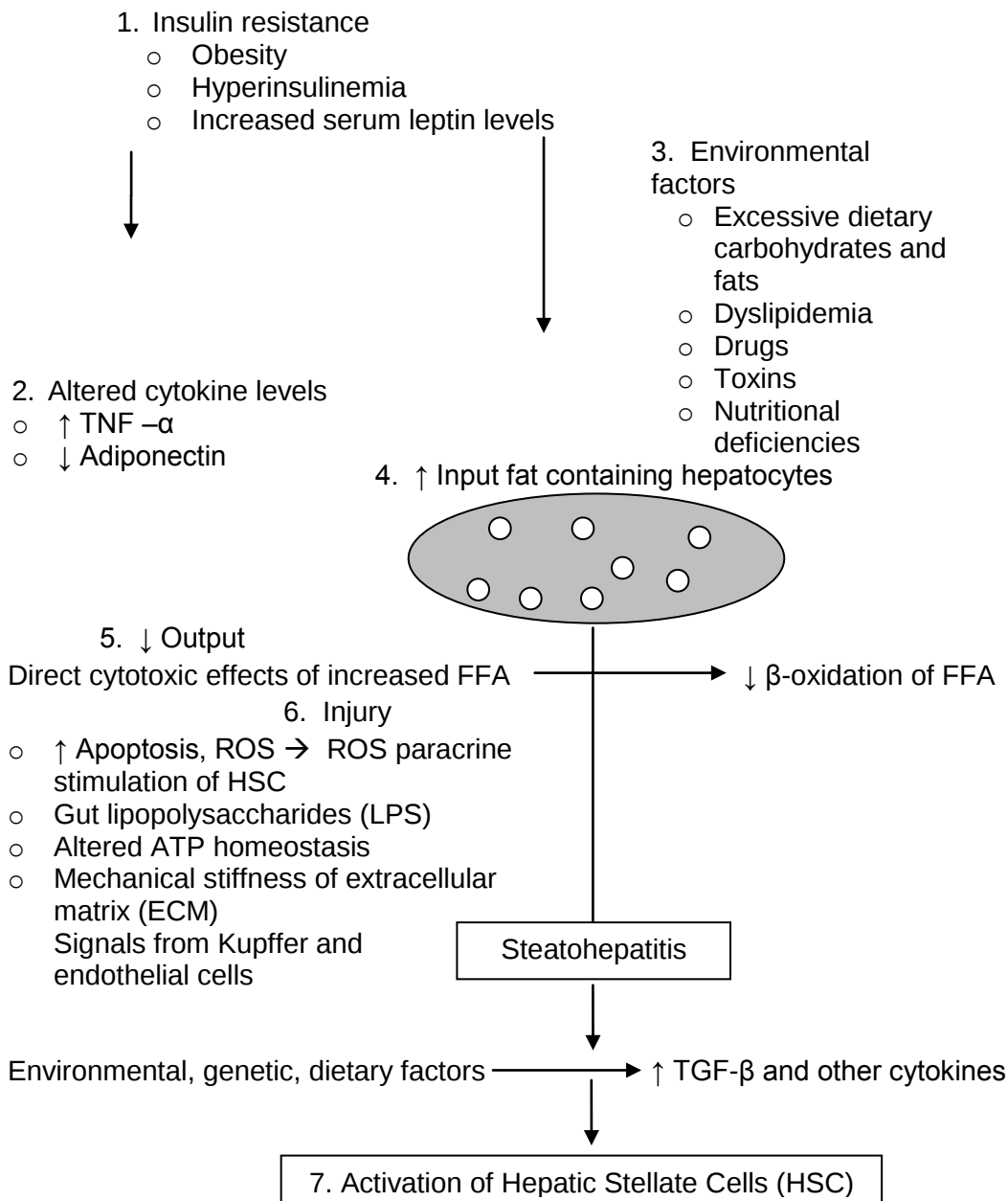
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Non-Alcoholic Fatty Liver Diseases (simple steatosis and non-alcoholic steatohepatitis)

Pathogenesis of fatty liver disease (NAFLD)



- Hepatic stellate cells (HSC)
 - Activation
 - The HSC is the central effector in hepatic fibrosis
 - HSC undergoes activation through a two phase process
 - Initial liver injury results in hepatocyte cell apoptosis with generation of apoptotic bodies, reactive oxygen species (ROS), and paracrine stimulation of HSCs.
 - LPS from the gut also stimulate HSCs.
 - There are 4 main pathways for the activation of HSCs.
 - Growth factor signaling
 - Fibrogenic signaling pathways
 - TGFB1
 - CTGF/CCN2
 - Adipokine signaling pathways
 - Leptin
 - Jak, PPAR γ
 - Neuroendocrine pathways
 - Cannabinoid receptor signaling
 - Opioid signaling
 - Serotonin
 - Thyroid hormones
 - In the initial phase, the hepatocyte becomes sensitized to additional activation by upregulating various receptors.
 - The hepatocyte begins to secrete autocrine growth factors, chemokines, and ECM.
 - Activation → down-regulation of inhibitory MHC class I molecules

- ↓ lipid droplets from HSC
- ↑ PDGFR
- Maintenance
 - The perpetuation phase is the maintenance of HSC activation.
 - This maintained HSC activation involves changes in HSC proliferation, chemotaxis, fibrogenesis, and contractility.
 - Fibrocytes derived from the bone marrow transdifferentiate into myofibroblasts, and may increase ECM production.
 - Increased ECM enhances mechanical stiffness of the ECM can be sensed by and activate HSCs.
 - The contribution of dendritic cells to fibrosis is not well understood, but may include NK cell-mediated HSC killing.

Abbreviations: FFA, free fatty acids; HSC, hepatic stellate cell; ROS, reactive oxygen species

Adapted from: Lee UE, et al. *Best Practice and Research Clinical Gastroenterology* 25: 196, Figure 1.

Regulated changes in gene expression during activation of HSCs

- Transcription factors and targets (modulation of the activity of transcription factors)
 - Transcription factors which activate the transcriptional targets of HSCs: Ets-1, Mef 2, CREB, EGR-1, vitamin D receptor, Foxf1, Jun D, and C/ERPB
 - HSC activation: α_1 and α_2 chains of type I collagen – α – SMA, TGF β 1, TGF receptors MMP-2, and TIMPs I and 2
 - HSC inactivation (anti-fibrotic) – Lhx2 (LIM homeobox gene 2) - FoxO1 (forkhead box gene, group O)
 - Development and differentiation (factors expressed by HSCs)
 - Dominant – positive

- b HLH (basic helix-loop-helix transcription factors)
- E box DNA hexanucleotide sequence for b HLH binding
- Myo D, SREBP-1c, C-Myb and C-Myc
- Dominant – negative (antifibrotic)
 - I d proteins
 - C/ERP α
- Nuclear receptors
 - Retinoid responsive RXR and RAR.
 - FXR (farnesoid X receptor)
 - RXR and FXR dimerize after “sensing” bile acids.
 - The dimerized RXR and FXR activate SHP.
 - SHP suppresses the expression of the collagen gene.
 - PXR (pregnane X receptor)
 - PXR is activated by steroids, certain drugs, xenobiotics and antibiotics.
 - PXR dimerizes with RXR and induces cytochrome P450 enzymes.
 - PPARs (peroxisome proliferators-activated nuclear receptors)
 - ↓ HSC activation – expression of collagen gene.
- Epigenetic regulation (methylation of promoters)
 - “Epigenetics refers to changes in DNA methylation and associated histone modifications that influence the chromatin states and impact gene expression patterns, without affecting the sequence of the target DNA.”
 - Activation of HSC leads to “global” reduction in methylation.
 - ↑ CBF1 and MeCP2 result in ↓ IKB by way of promoter methylation.
 - IKB repression results in de-repression of NFkB activity.
 - ↑ NFkB increases the survival of HSCs.

- Micro RNA
 - “micro RNAs (mi RNAs) represent a family of small non-coding RNAs controlling translation and transcription of many genes”
 - TGFβ, LPS and NF-κB down-regulate the miR-29 family of miRNAs
 - ↓ miR-29 enhances hepatic fibrosis (i.e. miR-29 is anti-fibrotic)
 - Post-translational regulation of transcription factors
 - Phosphorylation
 - Sumoylation
 - Prenylation
 - Acetylation
 - Glycosylation

Source: Lee UE et al., Best Practice & Research Clinical Gastroenterology 2011;25:195-206

CLINICAL PHYSIOLOGICAL CHALLENGE – Fatty liver

Case: A 58 year old “Cuddly” grandmother suffering from type II diabetes (insulin resistance) is noted to have an elevated serum AST and ALT. Abdominal ultrasound confirms the clinical suspicion of fatty liver

Questions:

- Give the pathophysiological steps leading to non-alcoholic fatty liver disease (NAFLD)
- Outline the initiation and perpetuation steps leading to steatohepatitis and fibrosis
- “Go for Purple”: List the regulated changes in gene expression during activation of HSC (hepatic stellate cells)

Polycystic Liver Diseases (PLDs)

➤ Definition

- PLDs are disorders of the cholangiocyte which signal the formation and growth of liver cyst.

CLINICAL PHYSIOLOGICAL CHALLENGE – Polycystic Liver Disease

Question: Give 5 steps involved in the pathogenesis of PLD.

Answer:

- Malformation of the ductal plate through an altered development program of the biliary ducts.
- Changes in Ca^{2+} and cAMP, lead to abnormal function of cilia.
- Changes in fluid secretion by the epithelia through CFTR (cystic fibrosis transmembrane conductance regulator)
- Increased proliferation of cholangiocytes through IL-6, EGF (epidermal growth factor), VEGF (vascular endothelial growth factor) angiopoietin-1, and IGF-1 (insulin-like growth factor-1).
- Autocrine and paracrine angiogenic signaling, by factors which stabilize or phosphorylate HIF (hypoxia-inducible factors)-1 α by way of mTOR or Raf / mitogen-activated protein kinase (MEK) / ERK.
- Remodeling of extracellular matrix (ECM)
- MMP (matrix metalloproteinase)-2 increases activity of portal myofibroblasts to allow for expansion of cysts.

Adapted from: Strazzabosco M, et al. *Gastroenterology* 2011; 140: 1855-59.

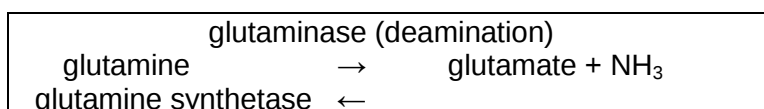
Hepatic Encephalopathy (HE)

Useful background: Q&As

Q. Outline the contribution of the small and large intestine, liver, skeletal muscle, kidney and brain in patients with liver failure and HE.

➤ Small bowel and large intestine

- Dietary amino acids and urease-positive bacteria → glutamine
- Uptake of glutamine



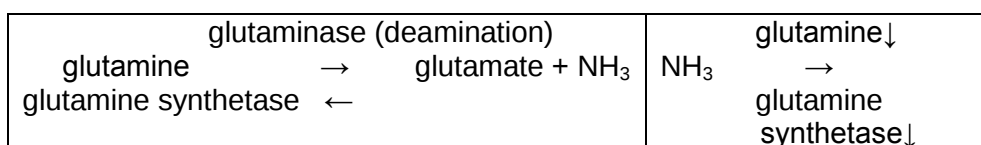
- Activity of gut glutaminase is increased in liver disease.
- Increased production of ammonia by urease-producing bacteria in GI tract
- Increased production of ammonia and glutamate from increased action of intestinal glutaminase

➤ Liver

- Portosystemic shunting, by-passing portovenous system with less hepatic detoxification of ammonia via the urea cycle
- NH₃ → urea, periportal hepatocytes → glutamine, perivenous hepatocytes
- In presence of hyponatremia, myoinositol falls, with less compensation for ↑ intracellular glutamine

➤ Skeletal muscle

- Atrophy of skeletal muscles, with reduced muscle synthesis of glutamine, large nuclei and nucleoli, margination of chromatin → Alzheimer type II astrocytes
- Uptake of 50% of NH₃



➤ Kidney

- increased NH₃ production in presence of hypokalemia

➤ Brain

- Ammonia and glutamate normally converted to and detoxified to glutamine by glutamine synthetase in astrocytes
- In cirrhosis, increased brain blood flow and increased blood brain barrier permeability: ↑ brain ammonia system
- Abnormal form and function of astrocytes, with reduced glutamine synthetase and peripheral type benzodiazepine receptors (PTBR)
- Increased brain glutamine increases mitochondrial permeability, which leads to brain edema.
- Glutamate normally taken up by synaptic excitatory amino acid transporters; reduced glutamate uptake leads to the accumulation of extracellular brain levels of glutamate, with impairment of the glutamatergic neurotransmitter system.
- Hyperammonemia activates N-methyl-D-aspartate-nitric oxide-C-granulate cyclase (NMDA-NO-C6MP) signal transduction pathway, impairing memory, learning and sleep.
- ↑NH₃ ↑glutamate cross BBB, and causes astrocyte swelling and cerebral edema
- In presence of hypokalemia and metabolic alkalosis, NH₄ → NH₃, which crosses BBB
- Plasma NH₃ > 150 μmol is associated with brain herniation
- CNS neurotransmitter disorder

Useful background: A grading of the mental state of persons with HE.

Grade	Criteria
➤ 0 (MHE, sub clinical HE)	Impaired mental tasks (psychometric testing speed of visual perception, and attention)
➤ I	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition; sleep-wake disorder; tremor

- II Lethargy or apathy; minimal disorientation of time or place; subtle personality changes; inappropriate behavior; impaired performance of subtraction
- III Somnolence to semi-stupor, but responsive to verbal stimuli; confusion, gross disorientation
- IV Coma (unresponsiveness to verbal or noxious stimuli)

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1966; and 2010, pg. 1545.

CNS neurotransmitters in HE

Neurotransmitter system	HE
○ Glutamate	▪ ↓ glutamatergic function
○ GABA/BZ	▪ ↓ receptors ▪ ↑ endogenous BZs
○ Dopamine/Noradrenaline (motor/cognitive)	▪ ↓ false neurotransmitters
○ Serotonin (Arousal)	▪ ↑ serotonin turnover, synaptic defect

Abbreviations: BZ, benzodiazepine; GABA-γ-aminobutyric acid

Useful background: Q&As

Q. Give the clinical neurological deficits in minimal hepatic encephalopathy (MHE).

- Affective/ emotional
- Behavioral
- Cognitive/ memory/ attention
- Language and verbal skills are relatively spared

Q. Give 4 important areas of assessment of the patient with possible MHE.

- Exclude other causes of metabolic encephalopathy
- Exclude possible precipitating factors of HE
- Altered neuropsychiatric testing
- Number connection tests (Trail Making)
- Visuomotor skills
- Mental tracking and concentration
- Digit symbol test
- Block design test
- Standardized test battery, the psychometric HE score (PHES)
- Digit span test (Weschler adult intelligence scale – passive auditory, working attention)
- Critical flicker frequency (correlates with PHES [Psychometric hepatic encephalopathy score])
- Quality of life measures: SE-36, chronic liver disease questionnaire (CLDQ)

Q. List 4 reasons to treat MHE.

- Improved cognitive function
- Quality of life
- Driving performance
- Performance in workplace
- Sleep
- Survival
- Prevent development of overt clinically evident HE

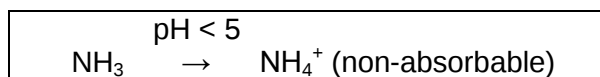
Adapted from: Ortiz M, et al. *J Hepatol* 2005;42 Suppl(1):S45-53. *Epub* 2004 Dec 28.

Q. Give the treatment of episodic and persistent HE, and provide the rationale for each treatment.

➤ Treat precipitants

- Increased ammonia production - excessive protein intake, constipation, GI bleed (20%), azotemia (30%), hypokalemia
- Increased protein catabolism - surgery, diuretics, arterial hypotension/hypovolemia,
- Malnutrition - skeletal muscle wasting, less muscle metabolism of NH_3
- Increased diffusion across BBB – alkalosis
- Synergistic effects of cytokines – infection (SBP) (10%)
- Altered brain function – sedative drugs, psychotropics, analgesics, benzodiazepines; hyponatremia; astrocyte swelling
- Dehydration – fluid restriction, diuretics, excessive paracentesis, vomiting, diarrhea (mechanism unknown)
- Hypoxia, anemia, fever, sepsis

- Metabolic:-K⁺↓ (50%), ↑BS, alkalosis; ↓hypoxemia, thyroid, dehydration
- Drugs (30%) - benzodiazapines, analgesics, interferon, alcohol, NSAIDs, acetaminophen
- Surgical shunting, anesthetic, TIPS
- Liver decompensation, HCC, PVT
- Surgery e.g., L-Tx (liver transplant)
- Lactulose (beta-galactosidofructose), lactic acid beta-galactosidosorbitol (traps NH₃) - enter colon, broken down by colonic bacteria to lactic acid, acetic acid acidification of stool pH < 5



- Hyperosmolar purgation, ↑ stool volume, loss of nitrogen compounds
- Neurotransmitters: flumazenil (a competitive GABA-benzodiazepine receptor antagonist) or bromocriptine
- Branched chain amino acids
- Measure and manage cerebral blood flow (CSF)
 - Intracranial pressure (ICP) monitoring, transcranial Doppler, jugular venous oximetry
 - Manage lactic acidosis and sepsis
 - 45° elevation of head of bed
 - Moderate hypothermia to reduce ICP and CBF, reduce arterial NH₃ and cerebral NH₃ uptake
- Manage circulatory effects
 - Fluid management, consider CVP monitoring

- Perform short synacthen test, and give GCS if adrenal insufficiency is present
- Inotropes: terlipressin (a vasopressin analog) or norepinephrine
- Albumin
- 'Biotics (pre-, pro- and synbiotics)
 - ↑ bacterial NH_3 utilization
 - ↓ pro-inflammatory response
 - ↓ gut permeability
 - ↓ bacterial translocation
- Extracorporeal liver assist devices (ELADs)
 - MARS (molecular absorbent recirculating system): providing counter-current hemodialysis against albumin and biocarbonate circuits
 - SPAD (single-pass albumin dialysis): counter-current albumin dialysis against high blood flow in a fibre hemodin filter, and continuous veno-venous hemofiltration
 - Prometheus R system, direct albumin adsorption through a specific polysulfur filter
 - Enteral feeding/TPN
- Orthoptic liver transplantation
 - ↑ lactobacillus spp., ↓ urease-containing bacteria, ↓ NH_3 production by replacing urease-positive bacteria
 - ↓ production of potentially toxic SCFA (propionate, butyrate, valerate)
 - Removes shunted (non-detoxified blood)

➤ Driving license – psychometric testing

Adapted from: Fitz GJ. *Sleisenger & Fordtran's Gastrointestinal and Liver Disease: Pathophysiology/Diagnosis/Management* 2006 pg. 1971-1972.

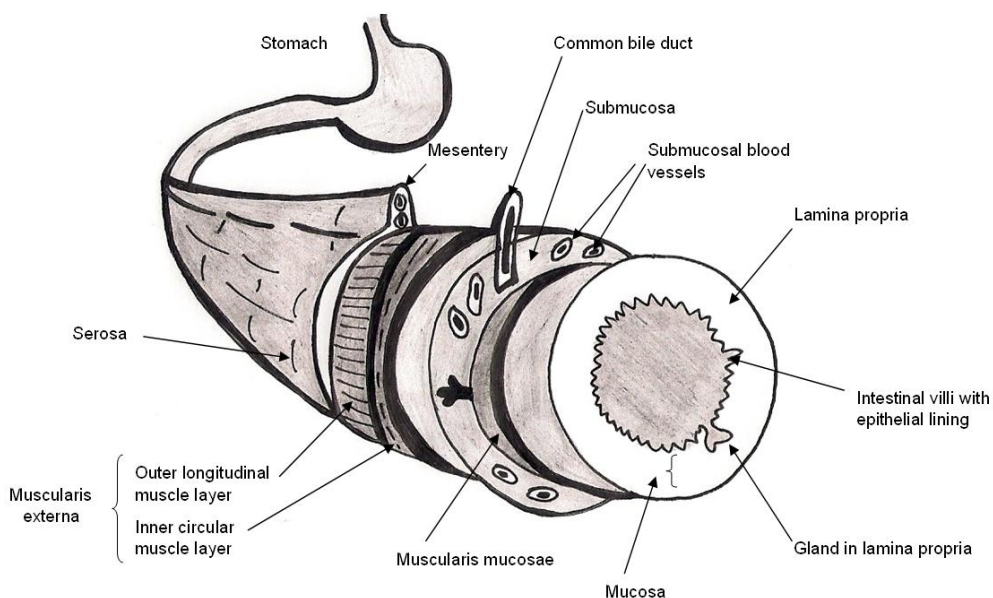
SMALL INTESTINE

The types of epithelial cells of the intestinal mucosa: enterocytes

Structure

- The main functions of the small and large intestine are the absorption of nutrients, electrolytes and water, as well as the secretion of water and electrolytes.
- The colon is about 5 feet long, and the small bowel is about 20 feet long.
- The mucosal surface area of the small and large intestine is increased macroscopically by the folds of Kerckring (valvulae conniventes) in the small intestine, and by the semilunar folds (Haustral folds) in the colon.
- The surface area of the absorptive cells at both sites is enlarged by the microvilli and by the crypts.

MACROSCOPIC VIEW OF THE WALL OF THE SMALL INTESTINE



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 41-2, page 885.

- Only the small intestine has a crypt-villus unit.
- Both the small and large intestine have five cell types in common:
 - absorptive cell (villus, in the small intestine, and surface cell in the colon),
 - goblet cell,
 - enteric endocrine cell (enterochromatin-like cell; ECL),
 - stem/progenitor cell,
 - undifferentiated crypt cell.
- Only the small intestine has Paneth cells at the base of the crypts.
- Paneth cells remain at the base of the crypt and make defensins, which are important in host defense against pathogen in the intestinal lumen.
- All of these cell types originate from the proliferative zone near the base of the intestinal crypt.
- The small intestine has relatively more villous epithelial cells, and the colon have relatively more goblet cells.
- Because of the folds, villi, crypts, and microvilli, the luminal surface areas of the small and large intestine are greatly increase to approximately 200 m² (said to be the approximate size of a tennis court) and 25 m² (about the size of four ping pong tabbles), respectively.
- The other cells migrate up the villus axis, mature during this process, and eventually undergo apoptosis and slough after three to five days at the tip of the villus.
- Absorption occurs predominantly in the small intestinal villous cells (enterocytes), and in the colonic surface absorptive cells (colonocytes).
- There is a spatial geometry of transport proteins along the crypt-villus axis of the small intestine, as well as along the small intestine from jejunum to ileum.
- In addition to the crypt-villus surface heterogeneity, there is segmental heterogeneity along the length of the intestine:

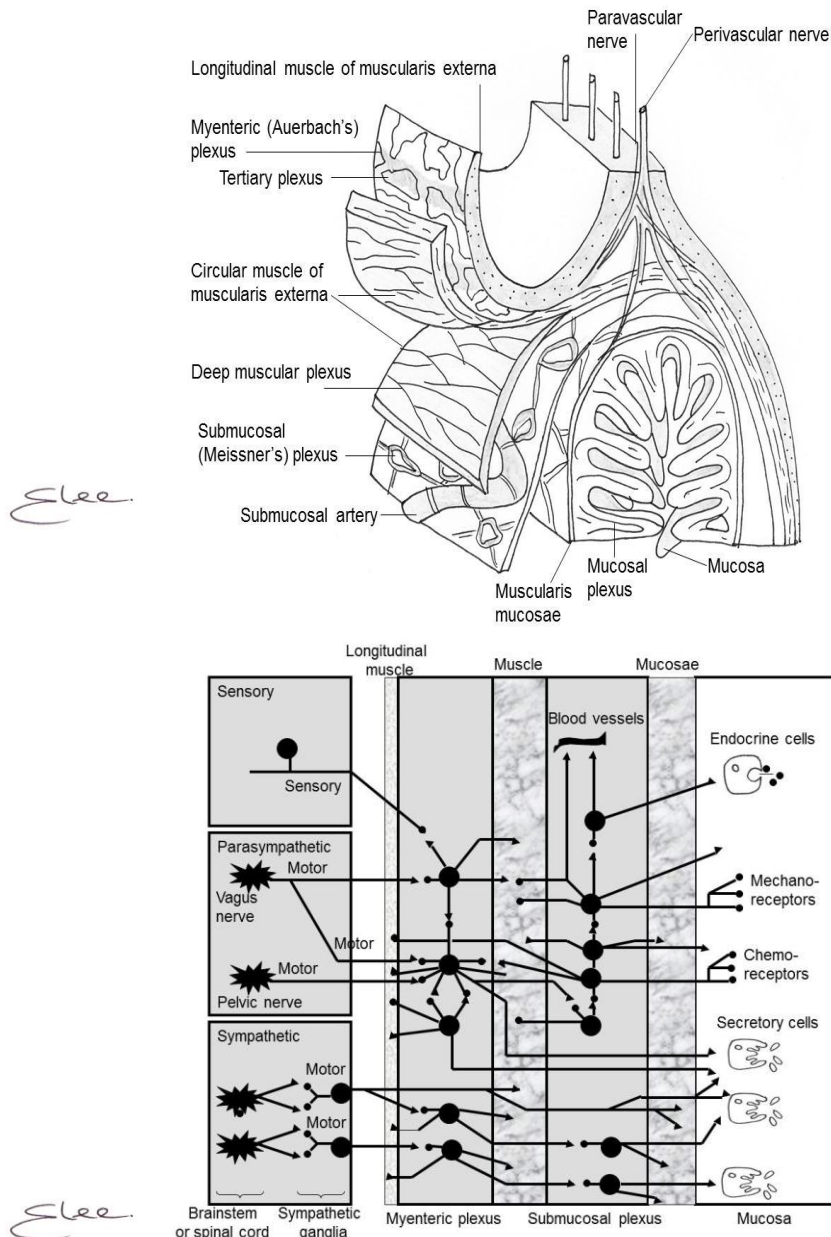
- the proximal intestine absorbs Fe^{+2} , Ca^{+2} , as well as
 - most dietary carbohydrates, lipids, amino acids, and
 - non-electrogenic and solute-coupled Na^{+} -absorption.
- The ileum absorbs
 - vitamin B_{12}
 - bile acids,
 - is a reserve for the absorption of nutrients not absorbed by the jejunum.
- Intestinal epithelial cells are structurally and functionally geared for vectorial transport.
- Some transport molecules are distributed at relatively constant concentrations along the axis,
 - Some exhibit a greater density in the base of the crypt.
 - Some exhibit a greater density towards the tip of the villus or surface.
- Only nonpolar (lipophilic) solutes freely cross a lipid membrane domain by simple diffusion.
- The transfer of ions and charged molecules necessitates specific transmembrane proteins to modulate entry into and exit from the cell.
- Ion-specific channels mediate membrane transport by facilitated diffusion.
- Carriers in the membrane undergo a conformational change.
- Active transport occurs against an electrochemical gradient.
- Active transport can be driven by adenosine triphosphate (ATP) (primary active transport, E1), or an ionic gradient (secondary active transport, E2).
- The Na^{+} pump on the BM maintains an electrochemical profile.

Small Intestinal Motility

- Functions
 - Mixing (churning), storage (resevoir), propulsion (peristalsis)
 - Preceding waves of relaxation followed by contraction of smooth muscle
- The submucosal (or Meissner's) plexus is located between the muscularis mucosae and the circular muscle of the muscularis externa.
- The myenteric (or Auerbach's) plexus is located between the circular and longitudinal layers of the muscularis externa.
- Meissner's and Auerbach's plexuses have ganglia.
- Three other plexuses are also present: mucosal, deep muscular, and tertiary plexus (in addition to Meissner's and Auerbach plexus):
- The plexuses contain the intestinal cells of the Cajal (ICC), the electrical pacemaker system of the gut intestinal muscle cell.
- The ICCs in the myenteric plexus (ICC_{MY}) between the inner circular and outer longitudinal muscles act as pacemakers.
- Electrical slow waves are generated, and spread through gap junctions to the ICCs within muscle (ICC_{IM}) as well as in the deep muscular plexus (ICC_{DMP}).
- The conduction is from nerve to ICC, and then through the electrical gap junctions to the myocytes.

➤ Enteric Nervous System (ENS)

Enteric Nervous System (ENS) of the Small Intestine



Adapted from: *Medical Physiology*, Figure 41-3, page 887, Second Edition, 2009

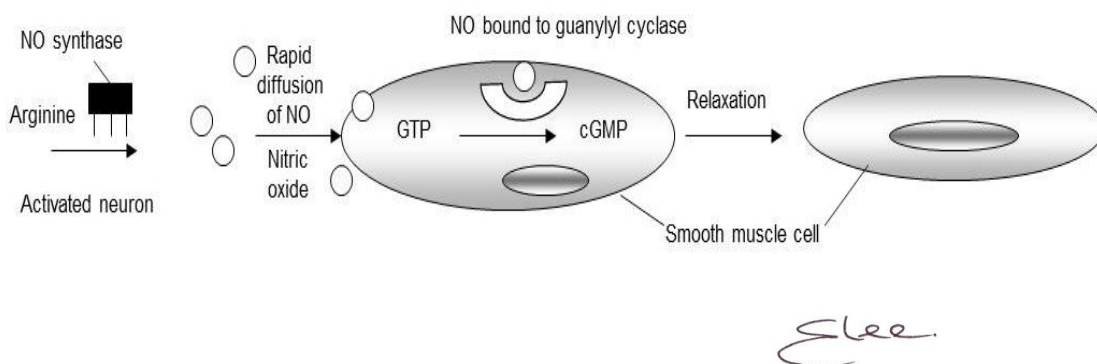
- The ENS is comprised of neurons with cell bodies in the wall of the intestine. The ENS consists of sensory neurons, interneurons, and motor neurons. Some sensory signals travel centrally from the ENS.
- Both the parasympathetic and the sympathetic divisions of the autonomic nervous system (ANS) modulate the ENS.
- The motor neurons of the ENS connect to the autonomic nervous system (ANS) which in turn connects to the central nervous system (CNS).
- Small intestinal sensory neurons pass through spinal or vagal routes to the CNS. More than 80% of the vagal fibers are efferent (motor).
- The smooth muscle acts as a syncytium, rather than as discrete motor units.
- Sphincters
 - Examples include
 - The upper and lower esophageal sphincter [UES, LES]
 - Pylorus
 - Sphincter of Oddi
 - Ileocecal sphincter
 - Internal anal sphincter (the external anal sphincter is comprised of skeletal muscle, not smooth muscle).
- The ganglia of the ENS are clusters of cell bodies which are in the submucosal or myenteric plexus.
- The interganglion fascicles (axons of motor neurons and interneurons) connect the ganglia of the submucosal and myenteric plexuses.
- The myenteric plexus itself has three networks: the primary, secondary and tertiary plexus.
- The afferent neurons in the myenteric plexus respond to chemical and mechanical stimulation of the muscle layer.

- Spinal afferents mediate pain.
- The spinal afferents are close to the perivascular nerves, and pass to the prevertebral ganglia, where they synapse on postganglionic sympathetic motor neurons.
- At the prevertebral ganglia, the perivascular nerves in turn pass along the splanchnic nerves in the thoracic spinal cord.
- There are sustained tonic contractions, as well as rhythmic alternating contractions and relaxations.
- There is normally tonic contraction of circular and longitudinal smooth muscle of the small intestine, with preceding relaxation stimulated from proximal food bolus or neurohormonal factors, and coordinated with proximal and distal contractions.
- Relaxations are due to membrane potential of smooth muscle (V_m) being low, and creating slow wave activity.
- When V_m exceeds the threshold to produce an action potential, there is a muscular contraction.
- Mucosal “sensing” of nutrients provides feedback control on both gastric acid and small intestinal motor function.
- Motor function in the small intestine provides time for mixing, digestion and absorption, as well as for the movement of chyme along the small intestine.
- This movement provides exposure of the chyme to the generous surface area of the intestine, thereby allowing for ~80% to 90% absorption of nutrients and electrolytes and water.
- Non-propulsive mixing (churning) in the antroduodenal cluster unit and small intestine arise from contraction of the inner circular smooth muscle.
- This churning facilitates digestion and absorption after the intake of food and fluid.
- After the intake of food (fed state), vagal stimulation and food itself (through myogenic, neurogenic and hormonal factors) stimulate peristalsis (propulsion).

- The peristaltic wave arises from proximal inner circular muscle contraction and outer longitudinal muscle relaxation, in conjugation with more distal relaxation from circular muscle relaxation and longitudinal muscle contraction.
- Rhythmic contractions of the small intestinal electrical and motor activity form the migrating motor complex (MMC).
- There are four phases of MMC: I) quiet; II) increasing electrical and motor activity; III) peak electrical and motor activity and IV) decreasing electrical and motor activity.
- MMCs occur every 90-120 minutes, and stop when a person eats.
- 15% of MMCs arise from the stomach, and the remainder begin in the proximal small intestine.
- During fasting, the stomach is cleared of particles bigger than 2 mm, and the small intestine is cleared during the fasting interval of MMC activity.
- The prokinetic (peristalsis enhancing) duodenal mucosal hormone motilin is released just before MMC phase III.

➤ Smooth muscle relaxation

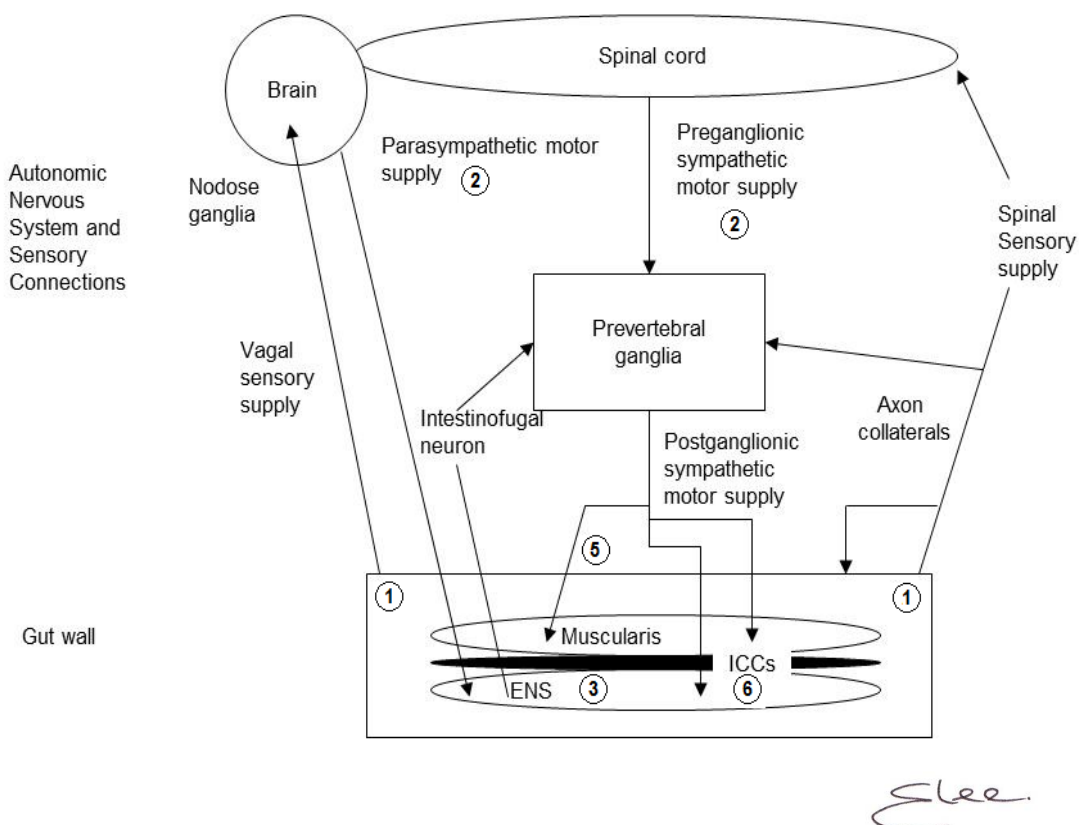
NITRIC OXIDE (NO) SIGNALS SMOOTH MUSCLE RELAXATION



Abbreviations: NO, nitric oxide

Adapted from: *Slisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 1.6, page 12, Ninth Edition, 2010

SMALL INTESTINE MOTOR CONTROL SYSTEM



Abbreviations: CNS, central nervous system; ENS, enteric nervous system; ICC, intestinal cells of Cajal

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 97.3, page 1646, Ninth Edition, 2010.

1. Sensory afferents

- Mucosal afferents respond to absorbed nutrients, as well as the transmitters released from both the epithelial enterochromaffin-like (ECL) cells mechanical deformation of the mucosa, and from immunocompetent cells.
- Serosal afferents respond to distortion of the mesentery or serosa.
- Muscular afferents have low thresholds to respond to contraction or distension.

- The intramuscular arrays (IMAs) are nerve terminals in the longitudinal and circular muscle layers, and act as tension receptors.
- The intraganglionic laminar endings (IGLEs) are in the vagal afferent terminals in the myenteric plexus.
- Single IGLEs may have mechanosensitivity, whereas multiple IGLEs detect shearing forces between the circular and longitudinal muscles.

2. Autonomic nervous system

- Parasympathetic
 - The parasympathetic supply to the intestine is cholinergic, cranial and stimulatory to smooth muscle in the intestine.
 - Vagal afferents are involved in physiological regulation.
 - The cell bodies of the parasympathetic supply are in the dorsal motor nuclei of the vagus.
- Sympathetic
 - The sympathetic supply is adrenergic, and inhibitory to smooth muscle in the intestine.
 - The cell bodies of the sympathetic supply are inhibitory except at the sphincters where the sympathetic supply is stimulatory.
 - The primary sympathetic motor neurons are in the intermediate horn of the synapse, and the second order neurons are in the prevertebral ganglia.
 - These synapse with ENS motor neurons in the intramural plexus.
 - There is likely some connection between the vagal/parasympathetic and the spinal/sympathetic control systems.

3. Enteric nervous system (ENS)

- Because of the extensive afferent interneuronal connections and constant sensory feedback, the ENS may control long segments of the intestine without any extrinsic input.

- The efferent output from the ANS (autonomic nervous system) may modulate the ENS.

4. Neurotransmitters

- Nitric oxide (NO), synthesized from arginine by nitric oxide synthase (NOS), diffuses across the plasma membrane into the smooth muscle cells
- NO binds to and activates guanylyl cyclase, which converts GTP to cGMP
- cGMP causes smooth muscle relaxation.
- The main excitatory neurotransmitters for small intestinal motility are
 - Excitatory acetylcholine (ACh; fast)
 - Substance P (SP; slow)
 - NO (fast)
 - ATP (fast)
 - VIP (slow inhibitory)

5. Smooth muscle contraction and relaxation

- Excitatory motor neurons release acetylcholine (ACh), which acts on M2 and M3 cholinergic receptors to produce an inward current.
- This current depolarises and opens the L-type Ca^{2+} channels.
- NO and VIP from inhibitory neurons activate receptor as well as non-receptor mechanisms in the ICC_{IM}, opening K^{+} channels and closing Ca^{2+} channels.
- This opening of K^{+} and closing of Ca^{2+} channels counters the excitatory effect of ACh on muscle contraction.
- Smooth muscle cells within each muscle layer (inner circular layer encircling the lumen, outer longitudinal layer extending axially, and the muscularis mucosae) form a syncytium.
- In the syncytium, each myocyte is connected electronically with each other through electrical gap junctions.
- The mechanical connection between myocytes is provided by the intermediate junctions.

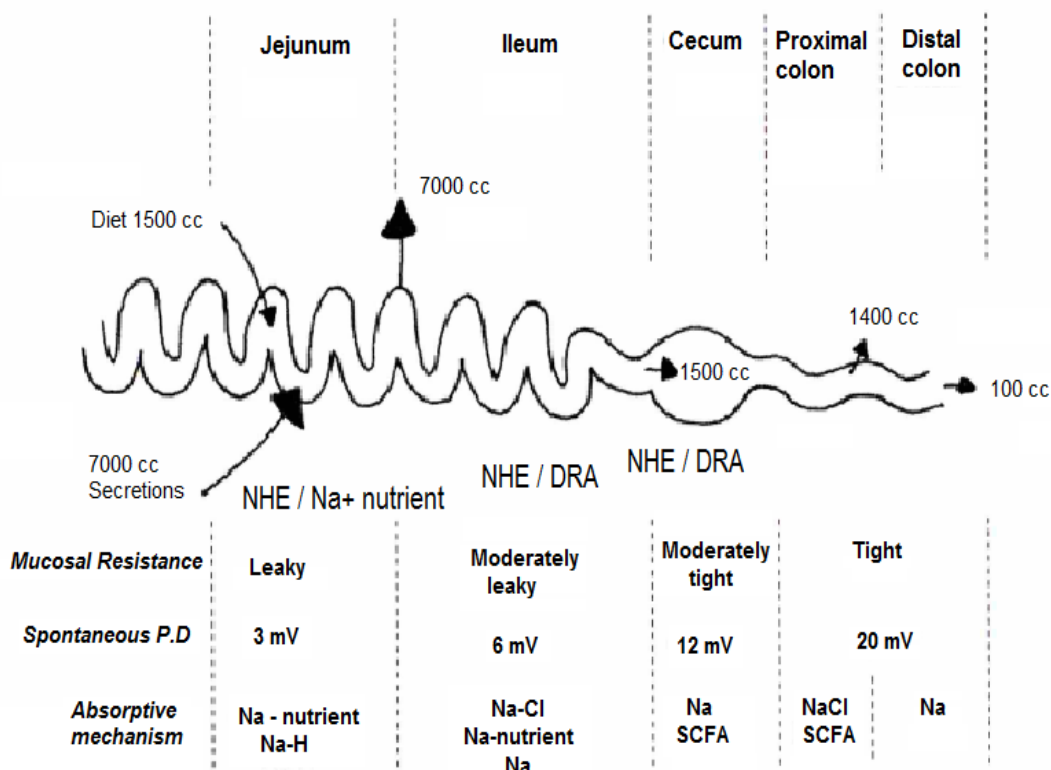
- Traditionally, the ICCs have been thought to generate the electrical slow wave and to transmit to the myocytes the neural inhibitory or excitatory signals.
- The intestinal cells of Cajal (ICC) lie close to the myocytes and to the nerve axons forming electrical gap junctions.
- When the actin (thin filaments) and myosin (thick filaments) in the myocytes contract, the smooth muscle cell shortens.
- The overall mechanical connection between large groups of myocytes is provided by a connective tissue stroma.
- The two patterns of intestinal motility include peristalsis, and the interdigestive motor cycle (IDMC).
- The IDMC produce the MMCs during the postprandial interval.
- Clinically muscle contractions may be assessed from changes in the pressure in the intestinal lumen.
- Wall motion of the intestine may be assessed by ultrasound, MRI, or by multichannel intraluminal impedance (MII) measurements.
- Small intestinal transit may be assessed by breath tests, drug pharmacokinetics, and by scintigraphic studies.

Absorption of Water

Intestinal Fluid Balance

- Water absorption is linked to the transport of sodium (Na^+) and nutrients, as well as to the permeability of the epithelial surface, as influenced by tight junctions (TJs).
- 8 to 9 litres of fluid flow through the small intestine each day.
- Salivary, gastric, biliary, pancreatic, and intestinal secretions make up the bulk of this amount, with about 1.5 L arising from oral intake.
- Most intestinal fluid is absorbed in the small bowel, with approximately 1000 to 1500 ml of fluid crossing the ileocecal valve.
- The colon extracts most of this fluid, leaving 100 to 200 ml of unabsorbed water daily in the stool each day.

- The small intestine receives about 8.5 L of fluid per day from the following sources: food, 1.5-2.0 L; saliva, 1.5 L, stomach, 1.5-2.0 L, pancreas, 1.0-1.5 L, bile, 0.5 L, small intestinal secretion, 1.0 L.



Elee

Adapted from *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009, Figure 44-2, page 936; and *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 99-1, page 1678, Ninth Edition, 2010

- Of this approximately 8.0 L/day, 1.5-2.0 L enters the colon, thanks to the small intestinal fluid reabsorptive efficiency of about 75%.
- Of the 1.5- 2.0 L/day entering the colon, only about 0.1-0.2 L/day escapes absorption and is passed in the stool, giving an absorptive efficiency of 90%-95%.

- This means that the average daily stool output is only about 200 ml fluid and 50 g of food debris, desquamated mucosal cells, and bacteria.
- A diseased process in the small bowel is likely to result in a large volume of diarrhea (“big gushes”), whereas a disease process in the colon is more likely to result in a small volume of stool (“little squirts”).
- Fluid and electrolyte secretion occur largely in the crypts of Lieberkuhn in the crypt-villus unit, and in the colonic crypts.
- The absorptive mechanisms in each segment of the gut differ, whereas chloride (Cl^-) secretion is found throughout the intestine.

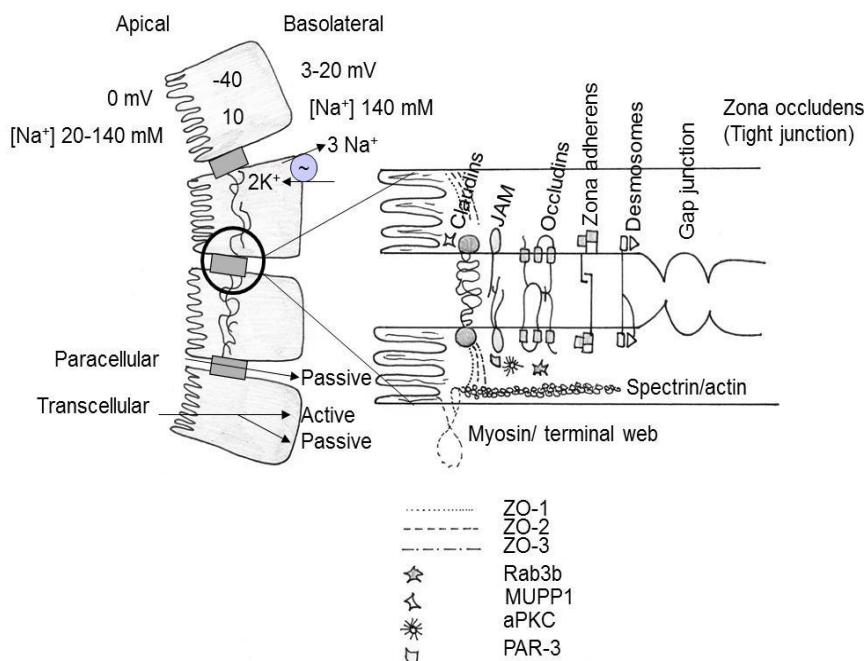
Water Absorption

- Water transport may be paracellular (through tight junctions), or transcellular.
 - The intestinal AM of the villi of the enterocytes absorb solutes such as glucose, and water by transcellular aquaporins in the membrane, and by paracellular movement across TJs.
 - Transcellular transport of water molecules occurs via channel proteins (aquaporins) or carrier proteins.
 - For example, the Na^+ - dependent sugar transporter in the intestinal brush border (apical) membrane (AM) by SGLT1 co-transport H_2O .
- Paracellular transport of water (H_2O)
- The transport nutrients and electrolytes across the BBM (brush border membrane) and then across the BLM (basolateral membrane) produce the osmotic and electrochemical gradients to provide for the passive absorption of H_2O .
 - The electrochemical gradient is achieved by the BLM Na^+ / K^+ ATPase.
 - The paracellular pathway is characterized by a series of structures which are defined by specific molecular distributions components of the tight junctions.

- In the enterocyte the tight junctions (TJs) separate the cell membrane into the brush border (apical) membrane (AM) and basolateral membrane (BM).
- This leads to an asymmetrical distribution of transporters.
- These two membrane domains have very different functional properties.
- The tight junction (aka zona occludens [ZO]) is a network of strands and grooves that consist of membrane proteins (e.g., occludins, claudins, and junctional adhesion molecules [JAMs]).
- These protein membranes attach to a group of scaffolding proteins (zonula occludens proteins [ZO-1, ZO-2, ZO-3] as well as multi-PDZ domain protein-1 [MUPP1]).
- These scaffolding proteins are linked to the cytoskeleton, which participate in vesicular transport (via monomeric guanosine triphosphatase [GTPase] of the Ras superfamily (Rab3b).
- The scaffolding proteins also participate and in the activation of signaling molecules that regulate junction assembly (partition-defective protein, PAR-3 and -6, and atypical protein kinase C, [aPKC]).
- As one progresses down the intestine, the junctions between cells become progressively 'tighter', so that their permeability to water becomes lower.
- When the intestinal villus enterocytes absorb solutes such as glucose, water is also absorbed by transcellular aquaporins and by paracellular processes (across TJs).

Architecture of intestinal epithelia

- Adhering junction
 - Cadherins
 - Actin filaments
- Gap junction
 - Connexons
- Tight junction (TJ)
 - Groove
 - Ridge
 - Claudins (transmembrane proteins)
- Desmosomes
 - Cadherons
 - Plaque



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- Cadherins span the paracellular pathway across the zona adherens (ZA).
- Cadherins are responsible for cell-cell attachment and maintenance of cell polarity.
- Desmosomes are cadherin-like molecules that are linked to intermediate filaments.
- Molecules associated with the zona adherens (including rab, SRC, and yes) are involved in intracellular signaling through second messengers.
- Cadherins bind to catenins, which are linked to the actin cytoskeleton by way of an additional family of molecules, including radixin, vinculin and α -actinin.

- Gap junctions are an assembly of membrane spanning proteins called connexins.
 - Connexins allow the exchange of small molecules between neighboring enterocytes.
 - When solute exits across the BM of the enterocyte and into the restricted basal space of the lateral intercellular spaces, the fluid in the interstitial space becomes slightly hypertonic.
 - These osmotic gradients are sufficient to draw water from the intestinal lumen across the TJs, or through water pores in the AM and BM.
 - The TJs are a network of strands and grooves (occludins) attached to a group of membrane proteins, which are then linked to the cytoskeleton of the enterocyte.
- The role of Na^+ transport in transcellular H_2O absorption
- This negative cytoplasmic potential (~ -40 mV) acts as a driving force for Na^+ entry across the AM membrane:
 - Na^+ / nutrient- coupled transporters in the jejunum and ileum,
 - Na^+ / H^+ exchangers (NHE) in the jejunum and ileum,
 - Cl^- / HCO_3^- exchangers in the ileum and proximal colon (DRA),
 - ENaC (epithelia/ Na^+ channel) in the distal colon.

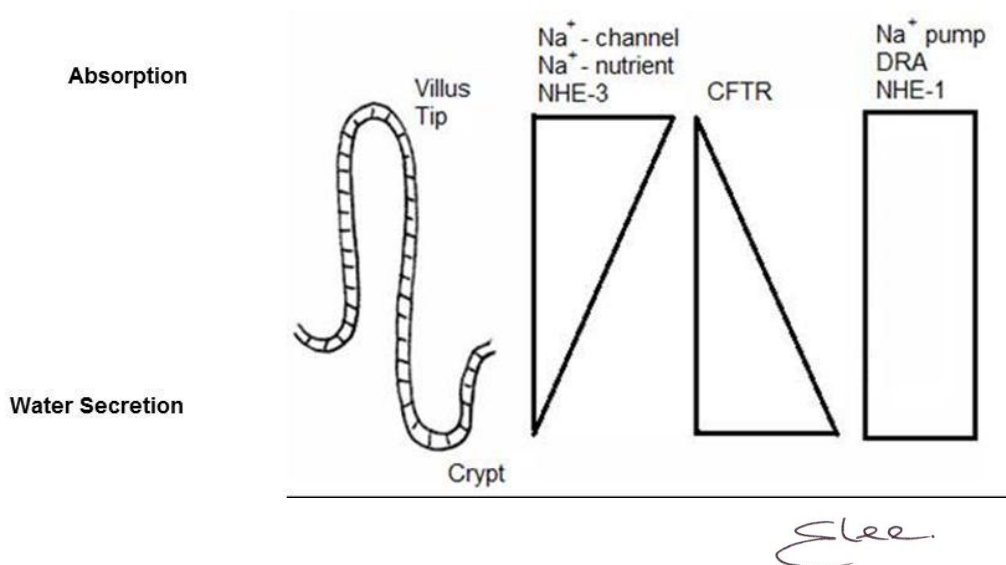
CLINICAL PHYSIOLOGICAL CHALLENGE - Diarrhea

Case: A 25 year old woman returns from a holiday in a Central American Country, complaining of watery (non-fatty and non-bloody) diarrhea. She is unable to tolerate drinking milk because of bloating, excess flatus and worsening diarrhea; but taking a mixture of sugar and salt improves her dehydration.

Question

- What is the normal process of absorption of salt and water?
- Explain how the intestine normally protects itself from luminal bacteria.
- What is the scientific basis for the tests used to diagnose SIBO (small intestinal bacterial overgrowth)?
- Explain her lactose intolerance
- Give the scientific basis for the use of oral rehydration solutions

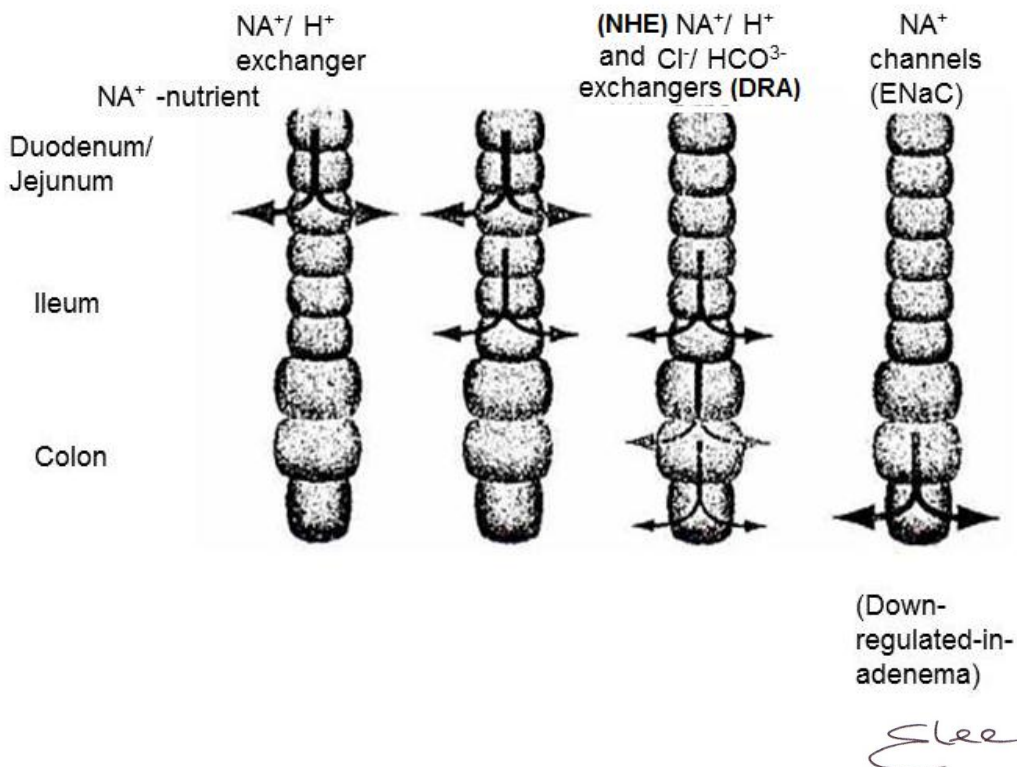
➤ Gradient of Na^+ transporters along crypt-villus axis



Abbreviations: CFTR, cystic fibrosis transmembrane receptors; DRA, Cl^- - HCO_3^- exchangers; NHE, Na^+ / H^+ exchangers

Adapted From: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 99-4, page 1678, Ninth Edition, 2010

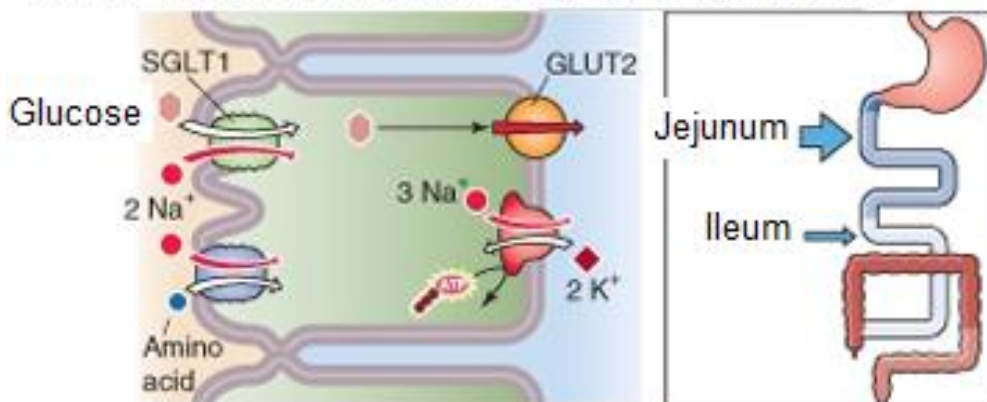
Gradient Na^+ absorption from proximal to distal intestine



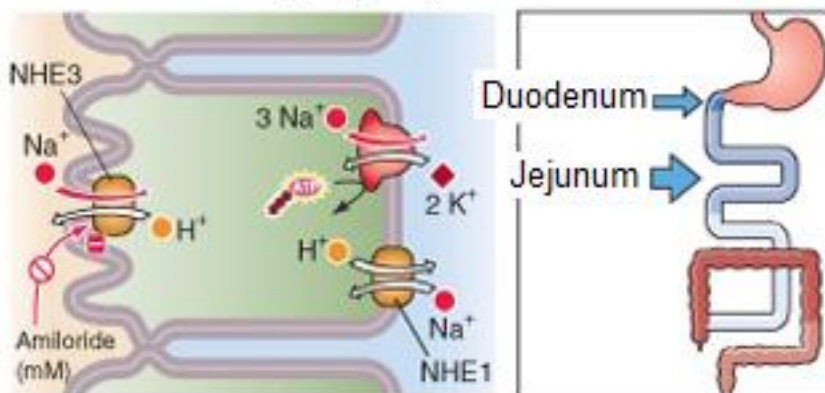
Abbreviations: NHE plus DRA, parallel $\text{Na}^+ - \text{H}^+$ (NHE) exchanger plus $\text{Cl}^- - \text{HCO}_3^-$ exchanger; DRA, down-regulated-in-adenoma [SLC 26A3])

Note: water absorption follows villus Na^+ absorption ; water secretion follows crypt Cl^- secretion

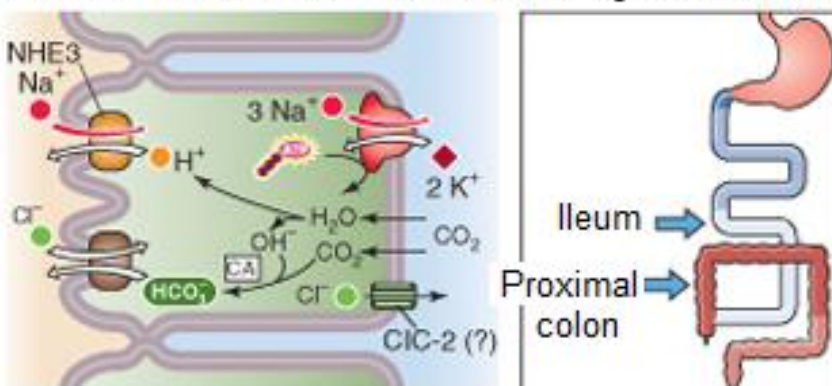
A. Na^+ / Glucose or Na^+ / Amino acid cotransporters



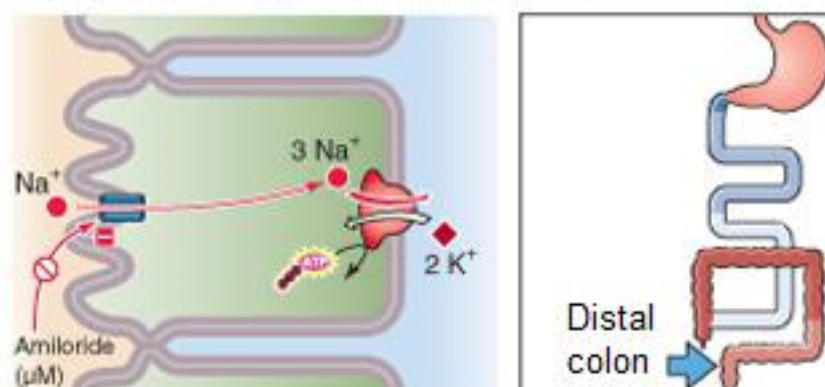
B. Na-H Exchanger (NHE)



C. Parallel Na-H (NHE) and Cl-HCO_3 Exchangers (DRA)



D. Epithelial Na^+ Channel (ENaC)



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-3, page 938.

➤ NHE and Na^+ nutrient cotransport in small intestine

- The Na^+/K^+ ATPase in the BM of the entire small intestine and colon exchanges 3 Na^+ molecules into the interstitial space for 2 K^+ transported into the cell.
- The lower intracellular Na^+ (about 15 mM or lower) generates an intracellular-negative membrane potential.
- This electrochemical drives the downhill entry of Na^+ from either the apical or basolateral side of the enterocyte (i.e., across the AM or BM).
- The Na^+ nutrient coupled transporters are not inhibited by increases in intracellular cAMP or Ca^{+2} .
- This forms the basis for the use of ORS (oral rehydration solutions) for persons with diarrhea (glucose plus Na^+ in water greatly accelerates the absorption of water).
- When the intestinal villus enterocytes absorb solutes such as glucose, water is also absorbed by transcellular aquaporins and by paracellular processes (across TJs).

➤ Digestive period

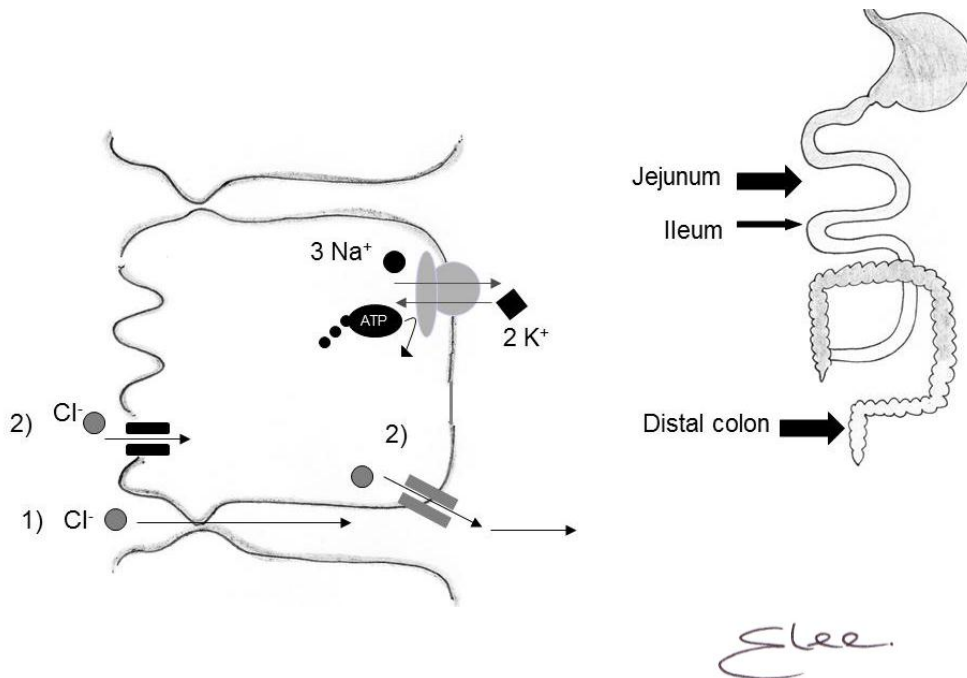
- With food intake, the nutrients in the duodenum and jejunum increase Na^+ and H_2O uptake across the AM.
- The increased uptake of Na^+ and H_2O is coupled to the movement of glucose or amino acids.
- If some glucose and/or amino acids reach the ileum, the solute-coupled Na^+ uptake occurs here as well.
- Also with food intake, the acid-stimulated secretin release from the duodenal S cells stimulates the pancreatic duct cells to secrete HCO_3^- - rich fluid.
- This excess of HCO_3^- in the lumen of the proximal small bowel as well as the increased intracellular H^+ stimulate the AM NHE (Na^+/H^+ exchangers, NHE_2 and NHE_3).
- The energy for $\text{NHE}_2/\text{NHE}_3$ arises from the intracellular Na^+ gradient created by the BM Na^+/K^+ pump.

- The nutrient - Na^+ pumps are energized by the Na^+ / K^+ pump in the BM of the enterocytes.
- Na^+ crosses the apical brush border membrane (AM) of the enterocyte, down an electrochemical gradient.
- The exit pathway across the BM is the – Na^+ , K^+ - ATPase (aka the Na^+ / K^+ pump) sodium pump.
- Na^+ / K^+ pumps move Na^+ into two restricted spaces.
- K^+ channels help maintain the electrochemical gradient.
- The NHE in the BM regulates the intracellular H^+ (pH_i) and has a much lesser role in creating a Na^+ gradient.
- The $\text{Cl}^- / \text{HCO}_3^-$ exchanger is also known as DRA (down-regulated-in-adenoma) or SLC 26A₃.
- These parallel AM Na^+ / H^+ (NHE) and $\text{Cl}^- / \text{HCO}_3^-$ (DRA) exchangers are influenced by small changes in the intracellular H^+ (pH_i).
- Intracellular cAMP, cGMP and Ca^{+2} act as intracellular messengers to reduce overall electroneutral NaCl absorption in the small and large intestines.
- Any Na^+ and H_2O which are not absorbed in the proximal small intestine are absorbed in the distal small intestine and the right side of the colon.
- In the lower small intestine and proximal colon, Na^+ absorption occurs through two coupled transporters, ($\text{Na}^+ - \text{H}^+$ [NHE] and $\text{Cl}^- - \text{HCO}_3^-$ [DRA]).
- In the distal colon, Na^+ is efficiently absorbed by membrane ENaCs (electrogenic Na^+ channels).
- The common exit pathway of Na^+ across the BM is the Na^+ / K^+ pump (Na^+ / K^+ ATPase).

Chloride (Cl^-) absorption

- Electroneutral NaCl absorption can mediate Cl^- absorption in the interdigestive period. pH_i couples the two exchangers. CA, carbonic anhydrase.

- Cl^- moves passively through the paracellular pathway or via cellular transporters.
- Passive Cl^- absorption – Tight Junctions and Chloride Channels

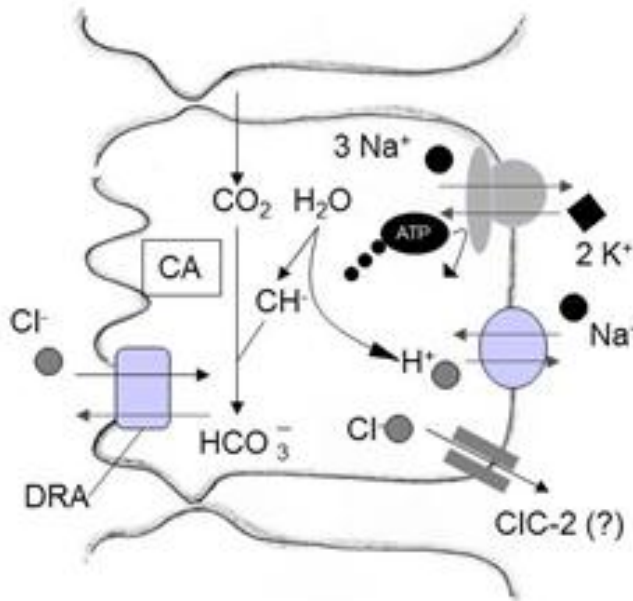


Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-4, page 940.

- 1) In voltage-dependent Cl^- absorption, Cl^- may passively diffuse from the intestinal lumen into the blood across the tight junctions, driven by the lumen-negative transepithelial voltage (paracellular route).
- 2) Alternatively, Cl^- may diffuse through AM and BM Cl^- channels.
- The electrochemical gradient for Cl^- across the Cl^- channels or TJs is derived from the electrochemical gradient for Na^+ .
- The electrochemical gradient for this passive movement of Cl^- is the lumen negative (PD) potential difference of -15 to -25 mV.
- This lumen negative -15 to -25 mV PD is produced
 - By the electrogenic transport of nutrient-coupled Na^+ movement in the small intestine, and

- By the electrogenic transport of Na^+ by ENaCs in the distal colon.
- o In the small intestine, this electrochemical gradient for Na^+ is produced
 - By the coupled AM nutrient and Na^+ uptake, and
 - By the BM Na^+ / K^+ pump.

➤ $\text{Cl}^- / \text{HCO}_3^-$ exchanger (DRA)

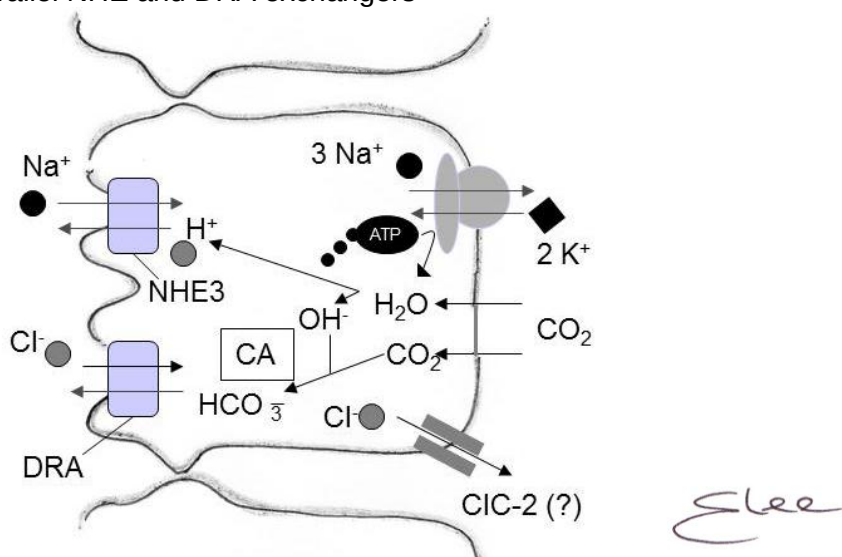


Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-4, page 940.

- o The contribution of the $\text{Cl}^- / \text{HCO}_3^-$ exchanger (in the absence of Na^+ / H^+ exchange) at these sites is PC (proximal colon) > DC (distal colon) = IL (ileum).
- o $\text{Cl}^- / \text{HCO}_3^-$ exchange in the PC and IL may be accompanied by electroneutral Na^+ / H^+ exchange (NHE).
- o In the absence of a parallel Na^+ / H^+ exchanger, electroneutral $\text{Cl}^- / \text{HCO}_3^-$ exchange at AM results in Cl^- absorption and secretion.

- In the upper small intestine, the $\text{Na}^+ \text{H}^+$ exchangers (NHE) are uncoupled (i.e. not coupled to another exchanger such as $\text{Cl}^- - \text{HCO}_3^-$) and are electroneutral (because no net transfer of charge occurs).
- NaCl absorption by the electroneutral processes of $\text{NHE}_2 / \text{NHE}_3$ and $\text{Cl}^- / \text{HCO}_3^-$ exchange are increased when the Ca^{2+} concentration in the cell falls.
- The K^+ entering the cell by way of the $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$ cotransporter leaves the cell across the BM IK1 and BK K^+ channels.

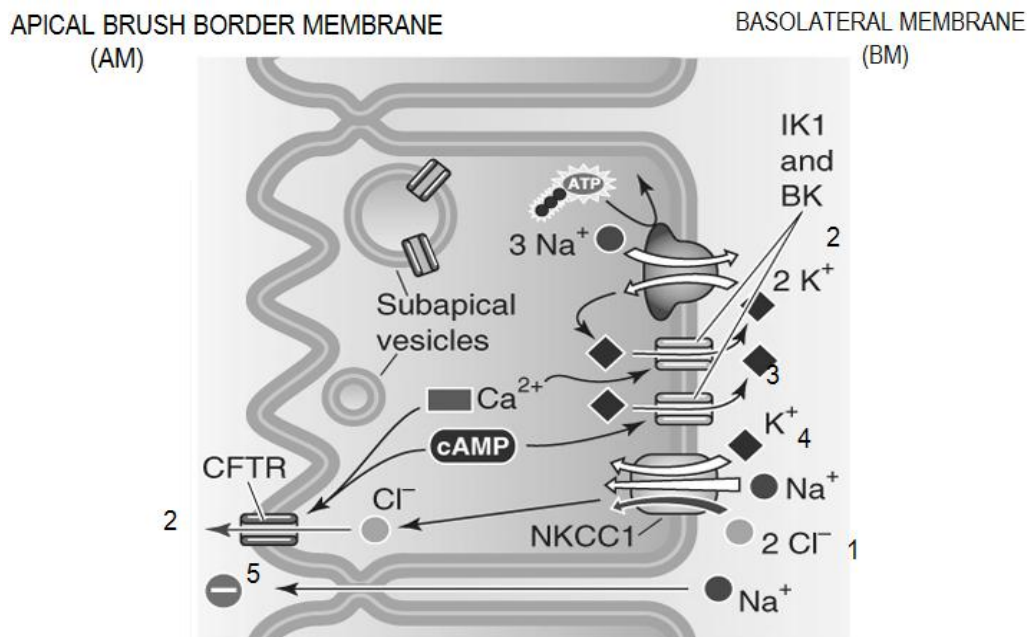
➤ Parallel NHE and DRA exchangers



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-4, page 940.

- The colon achieves electrogenic Na^+ absorption and K^+ secretion.

Chloride Secretion



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-5, page 941.

- Electrogenic Cl^- Secretion by Intestinal Crypt Cells.
 - Cl^- secretion is the basis of secretory diarrhea
 - Under basal (unstimulated) conditions, very little Cl^- is actively secreted by the crypt cells in the small and large intestine.
 - The thickness of the arrows in the inset indicates that the magnitude of the Cl^- secretory flux through this pathway is the same throughout the intestine.
 - 1) The BM $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransporter (NKCC1) in the BM of the crypt cells transports Cl^- into the enterocytes or colonocytes.
 - The $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ carrier couples the movement of Na^+ , K^+ , and Cl^- in a 1:1:2 electrochemical equilibrium.
 - The second messengers (cAMP, cGMP, Ca^{2+}) increase Cl^- secretion by the crypt enterocytes, and decrease NaCl absorption by the villous enterocytes.

- 2) Na^+ crossing into the cell BM by way of NKCCl is pumped out of the cell across the BM the Na^+ / K^+ ATPase.
- 3) K^+ entering the cell across the BM by NKCCl and Na^+ / K^+ ATPase leaves the cell across the BM K^+ channels.
- Secretion of Cl^- requires two active processes (the BM $\text{Na}^+ - \text{K}^+$ pump and the $\text{Na}^+ - \text{K}^+ - \text{Cl}^-$ transporter [NKCCl], as well as the BM IK1 channels and the BK channels on the AM CFTR).
- The BM entry and AM exit steps are integral to Cl^- secretion.
- 4) The Cl^- in the cell diffuses to the AM and exits the cell across CFTR (cystic fibrosis transmembrane receptor, a Cl^- channel)
- The high Cl^- in the intestinal lumen makes the transepithelial voltage negative (lumen vs. cell).
- 5) This voltage-negative lumen provides the electrochemical gradient for the passive movement of Na^+ across the paracellular TJs.
- As CFTR pumps Cl^- out of the cell, and Cl^- falls, more Cl^- , Na^+ and K^+ pass through NKCCl.
- In the jejunum, Cl^- diffuses across the TJs (paracellular route), driven by the lumen-negative transepithelial resistance.
- The paracellular pathway allows Na^+ movement from blood to lumen, driven by the lumen-negative transepithelial voltage.
- The Na^+ entering the cell from the blood through NKCCl exits across the BM Na^+ / K^+ pump.
- Na^+ from the blood also crosses the TJ (paracellular pathway) and into the lumen.
- This results in the lumen negative transepithelial voltage.
- The transepithelial resistance is maintained lumen-negative by the BM Na^+ / K^+ -ATPase.
- In the jejunum, Cl^- may also be absorbed passively through the channels in the AM and BM.

- In the colon, the electrochemical gradient is produced by ENaC.
- The AM ENaC in the proximal colon produces the electrochemical gradient for passive Cl^- absorption in the distal colon.
- Electroneutral Cl^- absorption may occur in the ileum and proximal colon by AM DRA ($\text{Cl}^-/\text{HCO}_3^-$ exchange), as well as by both AM $\text{Cl}^-/\text{HCO}_3^-$ and AM Na^+/H^+ exchange (DRA and NHE).
- Thus, the $\text{Cl}^-/\text{HCO}_3^-$ and Na^+/H^+ double exchange process is important in both the fasting or interdigestive period

Control of Chloride Absorption and Secretion

- Secretagogues
 - Open preexisting Cl^- channels, or
 - Cause subapical vesicles to fuse with the AM, thus creating new Cl^- channels.
- Increased $[\text{Ca}^{2+}]_i$ also stimulates PKC, as well as Ca^{2+} -calmodulin-dependent protein kinase (CaM kinase).
- There is a balance between fluid absorption and secretion in the small intestine. Reduced absorption or increased secretion of fluid may lead to diarrhea.

• Stimulate Absorption (Absorptagogues)

Inhibit cAMP	Coupled Transport	Other Pathways
○ Norepinephrine	Glucose, amino acids	Aldosterone, angiotensin
○ Epinephrine	Dipeptides/tripeptides	Glucocorticoids
○ Dopamine	Short-chain fatty acids	Somatostatin (blocks Ca^{+2} channels)
○ Enkephalins		GLP-2
○ NPY		
○ Somatostatin		

*Several agents activate multiple pathways.

Abbreviations: Ach, acetylcholine; ATP, Adenosine triphosphate; Ca_i , intracellular calcium [concentration]; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; EGF, epidermal growth factor; GLP-2, glucagon-like peptide 2; MAPK, mitogen-activated protein kinase; NO, nitric oxide; NPY, neuropeptide Y; TNF, tumour necrosis factor; VIP, vasoactive intestinal polypeptide

Secretion

Stimulate Secretion (secretagogues)

Increase cAMP	Increase cGMP	Increase Ca_i and/or Activate Protein Kinase C	Other Pathways (Tyrosine Kinase, MAPK, Gene Regulation)
○ VIP	NO	Ach	Interferon- γ
○ Adenosine	Guanylin	Serotonin	TNF- α
○ Prostaglandins	Uroguanylin	SP	Interleukin-1
○ Histamine		Histamine	Interleukin-6
○ Bradykinin		Bradykinin	Epidermal growth factor
		ATP	
		Adenosine	
		Neurotensin	

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➤ Tyrosine kinase

- The active protein kinases (PKs) increase the AM conductance to Cl^-
- The secretagogues activate PKs.
- Three PKs are involved in Cl^- secretion, PKA, PKC and PKG.

Protein kinase (PKs) involved in Cl^- secretion

PK	Activation	Second messenger
➤ PKA	○ Adenylate cyclase (AC)	- $\uparrow \text{cAMP}$
➤ PKC	○ Phospholipase C (PLC) ○ IP_3 ○ $\uparrow \text{Ca}^{2+}_i$	- Diacylglycerol ($\uparrow \text{DG}$)
➤ PKG	○ Guanylyl cyclase (GC)	- $\uparrow \text{cGMP}$

- These activated kinases stimulate net secretion of Cl^- by phosphorylating AM transporters as well as other proteins.
- Note that - The net result of the release of the secretagogues, changes in the second messengers, and activation of CFTR is the potent secretion of Cl^- and with it, Na^+ and water.
- Examples of these secretagogues would be
 - Bacterial enterotoxins (e.g. Heat stable E. coli toxins (aka STa); Yersinia toxin
 - Hormones and neurotransmitters
 - Immune cell products
 - Bile acids
- These transporters can be regulated by second messengers such as Ca^{2+} , cAMP (cyclic adenosine monophosphate) or cGMP (cyclic guanosine monophosphate).
- The DAG activates protein kinase C (PKC).
- Examples of these secretagogues would be
 - Cholera or heat labile toxins of Escherichia coli (E. Coli)
 - VIP
 - Histamine
 - Prostaglandins

➤ Signal transduction

- Receptor tyrosine kinases
 - Some ligand receptors have protein kinase activity, and their signaling does not include G protein molecular intermediaries.
 - These receptor tyrosine kinases (RTK) are proteins which act on the surface of cells, and are inserted into the cell membrane and span across the membrane.
 - Examples of RTKs which are relevant to GI include: VEGF.
 - Most RTKs undergo ligand binding to Ras.
 - Ras activate MAP kinase.
 - The RTK catalyze the transfer of phosphate from ATP to proteins upon which the phosphate acts.
 - Certain phosphorylated tyrosine kinase bind to Src homology regions 2 and 3 (SH2 and SH3 domains).
 - Any signaling protein which contains SH2 will become activated
- Coupling to G proteins
 - G proteins bind to GPCRs (G protein – coupled receptors) to activate adenylate cyclase (AC), guanylate cyclase, phospholipases and certain ion channels.
 - G proteins stimulate adenylate cyclase (Gs), or inhibit adenylate cyclase (Gi).
 - Gs forms a Gs-GTP complex.
 - The Gs-GTP complex activates AC, AC acts on ATP to form cAMP, and cAMP phosphorylates effector proteins.

Abbreviations: VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; IGF-1, insulin – like growth factor

➤ Intestinal Immune Cells

- Secretory and absorptive factors are released by intestinal immune cells, enteric endocrine cells, and by the ENS. These include:
 - Adenosine,
 - Arachidonic acid
 - Histamine
 - Bradykinin
 - Leukotrienes
 - Metabolites
 - Nitric oxide(NO)
 - Platelet activating factor (PAF)
 - Prostaglandin (PGs)
 - Reactive O₂
- These mediators also have an indirect effect on the epithelial cells by way of the enteric nervous system or a paracrine effect on another cell type such as myofibroblasts or intestinal smooth muscle.
- Immune as well as other cells in the lamina propria such as monophages, fibroblasts, mast cells, as well as neutrophils, release chemical mediators (such as histamine, prostaglandins, PAF, bradykinin).
- These mediators have a direct effect on the epithelial cells.
- Intestinal cells release an array of secretory factors, which can act either
 - Directly on the epithelium, or
 - Indirectly by stimulating the mesenchymal cells or enteric neurons to release prostaglandins (PAGES) or acetylcholine (Ach).
- Activation of mast cells in the lamina propria triggers the release of histamine.

- Histamine either
 - Directly affects epithelial cells, or
 - First stimulates an enteric neuron and thereby indirectly affects epithelial cells.
- There are interactions among secretory neurons and blood vessels, immune cells, and paracrine cells.

Immune Cell	Products
➤ Macrophages	– Prostaglandins – O₂ radicals
➤ Mast cells	– Histamine
➤ Neutrophils	– Eicosanoids – Platelet-activating factor
➤ Fibroblasts	– Eicosanoids – Bradykinin

Source: *Medical Physiology*, Table 44-3, page 945, Second Edition, 2009.

- The enteric neuron system (ENS) which has been stimulated by histamine modulates the
 - Epithelium (secretion),
 - Intestinal smooth muscle (motility), or
 - Vascular smooth muscle (blood flow)

CLINICAL PHYSIOLOGICAL CHALLENGE – Celiac Disease

Case: Celiac disease (CD) is a condition which affects the luminal GI tract from the esophagus to the colon, as well as the liver, gallbladder, and pancreas. Think of any untreated celiac patient you have seen with malnutrition and multiple nutrient deficiencies.

Question: What is the pathophysiology of the maldigestion and malabsorption of carbohydrate, peptides and amino acids, lipids, folic acid and calcium in CD?

➤ Enteric endocrine cells and GI peptide

- Intestinal fluid secretion is also altered by the endocrine system.
- When the body is dehydrated, angiotensin and aldosterone are released from the renin-angiotensin-aldosterone axis.
- Angiotensin and aldosterone are examples of absorptagogues.
- Angiotensin and aldosterone enhance
 - Electrochemical and Na^+ absorption in the small intestine,
 - Electrogenic Na^+ absorption in the colon.
- Somatostatin and glucocorticoids are also absorptagogues.
- In the distal colon, the mineralocorticoid aldosterone increases the activity of both ENaC and the Na^+/K^+ pump in the distal colon, thereby enhancing the electrogenic Na^+ transport in the distal colon.
- The Na^+ which has been taken up by ENaC is pumped across the BM of the distal colonocytes by the Na^+/K^+ pump.
- Glucocorticoids have a small effect on the mineralocorticoid receptor, as well as having a major effect on Na^+ /water absorption by way of its own receptor.
- The glucocorticoid receptor stimulates electroneutral Na^+ absorption in the small and large intestine.
- This paracrine effect is also seen with the paracrine effect of serotonin (5-HT) released by the enteric endocrine cells.

➤ Gastrointestinal Peptide Hormones Acting on Small Intestine and Colon

Hormone	Source	Action
○ Somatostatin	D cells of stomach and duodenum, islet cells of pancreatic islets	↑ Fluid absorption/↓ secretion ↑ Smooth muscle contraction
○ Vasoactive intestinal polypeptide (VIP)	ENS neurons	↓ Smooth muscle relaxation ↑ Secretion by small intestine
○ Guanylin	Ileum and colon	↑ Fluid absorption
○ Neurotensin	Endocrine cells, widespread in GI tract	↑ Histamine release
○ Substance P (SP)	ENS neurons	Neurotransmitter

Printed with permission: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Table 41-1, page 889.

➤ Enteric Nervous System (ENS)

- Neurons are responsive to intraluminal mechanical and chemical stimuli (e.g., food, bile acids, bacterial toxins, rotavirus).
- Interneurons in either the myenteric or submucosal plexuses also play a role in the response to the intraluminal and chemical stimuli.
- Secretory neurons that release acetylcholine (Ach) act on epithelial cells.

CLINICAL PHYSIOLOGICAL CORRELATION – More Diarrhea

Background: Diarrhea may result from an imbalance between intestinal secretagogues and absorptagogues. The treatment of diarrhea may include measures to normalize this imbalance.

Problem: Outline the role of the intestinal immune cells, endocrine cells and enteric nervous system in the control of fluid and electrolyte balance by the intestinal tract.

CLINICAL PHYSIOLOGICAL CORRELATION – Chloride Flux

Background: One process by which diarrhea occurs is through the decreased absorption of chloride (Cl^-) in the upper portion of the villus, and the increased secretion of Cl^- in the lower portion of the crypt-villus unit. The movement of Cl^- may be electroneutral or electrogenic and involves transporters and channels in the brush border membrane (AM) and the basolateral membrane (BM). Secretions of Cl^- is fundamental to the process of secretory diarrhea, such as occurs in cholera.

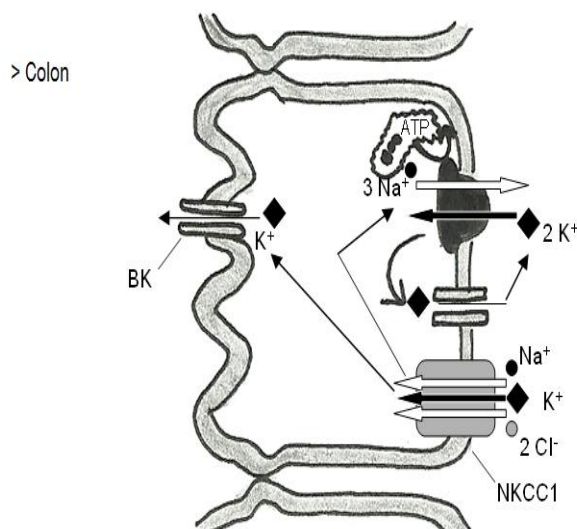
Problem: Draw a picture of Cl^- absorption and secretion from along the length of the small intestinal villus and in the colon.

Potassium (K^+) Absorption and Secretion

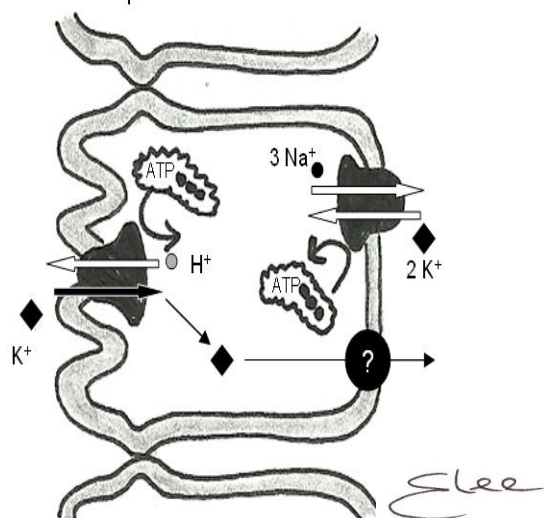
➤ Absorption

- In the small intestine, K^+ is passively pulled across the TJs or across the AM along with the water which is transported by the movement of solute and/or Na^+ .
- In the colon,
 - K^+ is absorbed into the colonocyte by the AM H^+-K^+ exchanger.

Active K^+ secretion



Active K^+ absorption



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 44-6, page 943.

➤ Secretion

- In the small intestine, K^+ is secreted from the enterocyte by AM K^+ channel (BK).
- K^+ is secreted from the colonocyte BM by BM NKCC1 ($Na^+-K^+-Cl^-$ cotransporter), and

➤ Control of K^+ absorption and secretion

- Aldosterone stimulates K^+ secretion in colonic surface epithelial cells.
- Aldosterone increases K^+ secretion both passively and actively;
- cAMP/ Ca^{+2} increase the activity of AM K^+ channels more than BM K^+ channels, resulting in net K^+ loss from the colonocyte.
- cAMP and Ca^{+2} stimulate K^+ secretion in the colonic crypts.

Absorption of Proteins, Peptides, Oligopeptides and Amino Acids

- Proteins are absorbed intact in minute amounts, or as peptides, oligopeptides and amino acids.

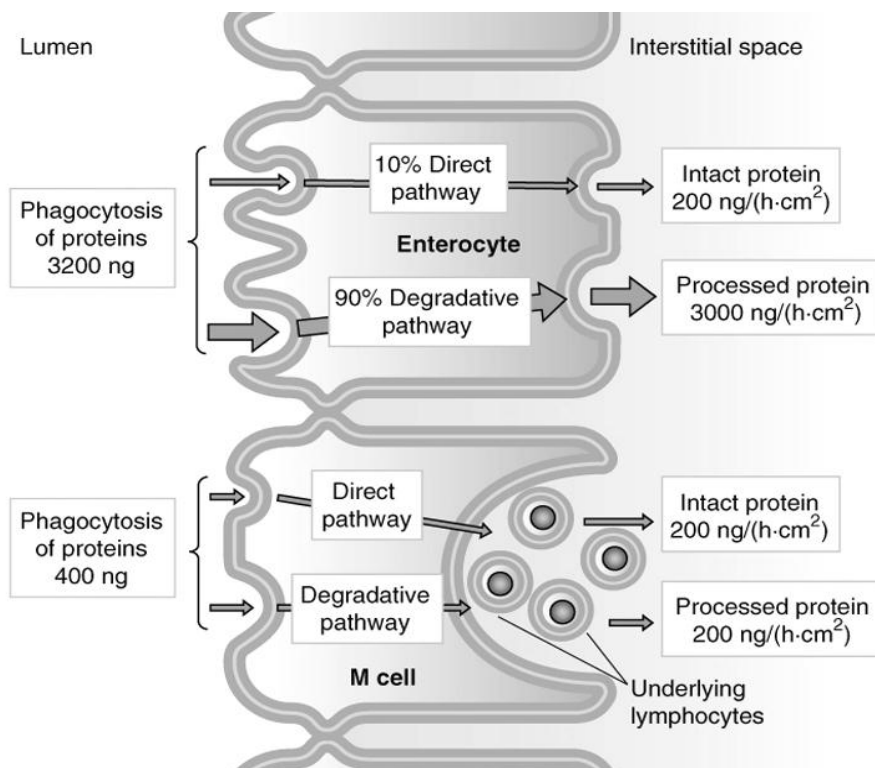
Source of Proteins

- About half of the proteins in the intestinal lumen are from sloughed GI tract cells as well as from secretions.
- Dietary protein digestion begins with gastric pepsin (pepsinogen activated by gastric HCL), and continues when the pancreatic proenzymes become active proteolytic enzymes.
- Animal protein is better digested than is vegetable protein.
- Protein, which contains abundant hydroxyproline is poorly digested.
- Food preparation and storage may reduce the digestibility of protein.
- Some AAs are not synthesized in the body, and as such are considered to be essential and must be supplied by the diet.

- Some AAs are synthesized in the body, but inadequate amounts are produced when the demand is high, and under these circumstances the AAs are said to be conditional.

Endocytosis of Intact Proteins

- Only very minute amounts of protein are absorbed intact, approximately 3600 ng/h-cm^2 of this 90% is phagocytosed by the enterocyte degradative pathway, and 10% by the direct pathway.
- Both enterocytes and specialized M cells can take up small amounts of intact protein by the process of endocytosis.
- The more abundant enterocytes endocytose much more total protein than do the less abundant M cells.
- The less abundant M cells take up relatively little intact protein, but approximately half of this emerges intact at the basolateral membrane.
- The M cells on top of the Peyer's patches (lymphoid follicles in the lamina propria) take up 400 mg/h-cm^2 of protein, 10% by the degradative pathway, and 90% by the direct pathway.
- The lysosomal proteases in the enterocytes degrade ~90% of this endocytosed protein.
- The processed protein does not result in an allergic reaction, while the intact protein does.
- The intact protein is processed by immunocompetent cells, which are transformed into lymphocytes, and an immune response begins.



Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 45-7, page 957.

CLINICAL PHYSIOLOGICAL CHALLENGE

Case: Celiac disease (CD) is a condition which affects the luminal GI tract from the esophagus to the colon, as well as the liver, gallbladder, and pancreas. Think of any untreated celiac patient you have seen with malnutrition and multiple nutrient deficiencies.

Question: What is the pathophysiology of the maldigestion and malabsorption of carbohydrate, peptides and amino acids, lipids, folic acid and calcium in CD?

- Digestion – Lumen: Pancreatic Proteolytic Enzymes

Peptides, Oligopeptides and Amino Acids

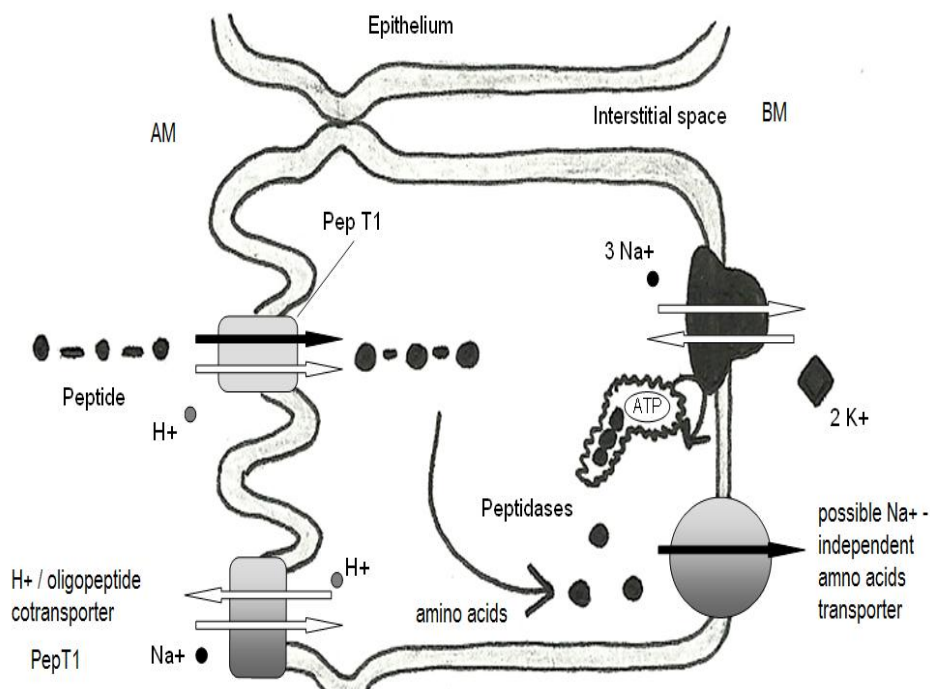
- A brief reminder: Recall from the previous chapter “The Pancreas”, the importance of the luminal steps of protein digestion, by the way of pancreatic proteolytic enzymes.
 - The initial digestion of nutrients in the mouth and stomach continues in the lumen of the upper small intestine, where it is furthered by the pancreatic and hepatobiliary secretions.
 - There are five proteolytic enzymes which break protein down to oligopeptides and to amino acids: (trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidase A and B.
 - All these proenzymes are activated by trypsin (“autoactivation”), which itself comes from trypsinogen.
 - Trypsinogen is also activated by jejunal enterokinase.
 - The three endopeptidases (trypsinogen, chymotrypsinogen and proelastase) produce oligopeptides of 2-6 amino acids (AAs).
 - The two exopeptidases carboxypeptidase A and B form single AAs.

○ Pancreatic Proteolytic Enzymes

Peptidase	Cleavage Sites	Products of Peptidases
➤ Trypsinogen	○ Internal bonds at lysine or arginine residues ○ Other pancreatic proenzymes	➤ Oligopeptides and proteolytic enzymes
➤ Chymotrypsin	○ Bonds at aromatic or neutral amino acid residues	➤ Oligopeptides
➤ Elastase	○ Bonds at aliphatic amino acid residues	➤ Oligopeptides
➤ Carboxy-peptidase A	○ Aromatic amino acids from C-terminal end of proteins and peptides	➤ Aromatic amino acids and peptides
➤ Carboxy-peptidase B	○ Arginine or lysine from C-terminal end of proteins and peptides	➤ Arginine, lysine, and peptides

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Table 45-2, page 956.

OLIGOPEPTIDE ABSORPTION



Elee

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 45-8, page 958.

- Oligopeptides (dipeptides, tripeptides and tetrapeptides) are actively transported across the enterocyte brush border (apical) membrane (AM) by the H⁺/oligopeptide cotransporter, PepT1.
- PepT1 is an active transport process driven by a H⁺ gradient.
- The H⁺ entering the enterocyte is removed by the AM NHE.
- The Na⁺ entering the cell by NHE is pumped across the BM by the Na⁺ / K⁺ ATPase.
- Cytoplasmic peptidases break down the di- and tri- peptides to single AAs.

- Peptidases in the AM break oligopeptides down to tripeptides, dipeptides, and AAs.
- The PepTi (H⁺/oligopeptide) cotransporter in the enterocyte AM transports di- and tri-peptides into the enterocyte cytosol.
- AAs are absorbed faster by PepTi than by the Na⁺/AA transporter.
- The AAs exit the enterocyte and pass into the portal circulation by way of one of the three Na⁺ - independent BB transporters.
- There are relative specificities of the intestinal peptide transporters for dipeptides and tripeptides

Dipeptides	Tripeptides
– L Form of amino acids in peptide	– D Form of amino acids in peptide
– Neutral amino acids in peptide	– Acidic or basic amino acids
– Long-side-chain amino acids in peptides	– Short-side-chain amino acids in peptides

Assimilation of oligopeptides

- Digestion of oligopeptides continues by peptidases at the enterocyte apical membrane and in the cytosol:

Peptidases in the AB/BBM and Cytoplasm of Villus Enterocytes

Peptidase	Cleavage Site	Products of Peptidases
• Brush Border Membrane Peptidases		
➤ Amino-oligopeptidases (at least two types)	○ Amino acids from C terminal end of 3 to 8 amino acid peptides	– Amino acids and dipeptides
➤ Aminopeptidase A	○ Dipeptides with acidic amino acids at N terminal end	– Amino acids
➤ Dipeptidase I	○ Dipeptides containing methionine	– Amino acids
➤ Dipeptidase III	○ Glycine-containing dipeptides	– Amino acids
➤ Dipeptidyl aminopeptidase IV	○ Proline-containing peptides with free α -amino groups	– Peptides and amino acids
➤ Carboxypeptidase P	○ Proline-containing peptides with free C terminal end	– Peptides and amino acids
➤ Gamma glutamyl transpeptidase	○ Gamma-glutamyl bonds and transfers glutamine to amino acid or peptide acceptors	– Gamma-glutamyl amino acid or peptide
➤ Folate conjugase	○ Pteroyl polyglutamates	– Monoglutamate
• Cytoplasmic Peptidases		
➤ Dipeptidases (several types)	○ Most dipeptides	– Amino acids
➤ Aminotripeptidase	○ Tripeptides	– Amino acids
➤ Proline dipeptidase	○ Proline-containing dipeptides	– Proline and amino acids

Abbreviation: BBM, brush border membrane

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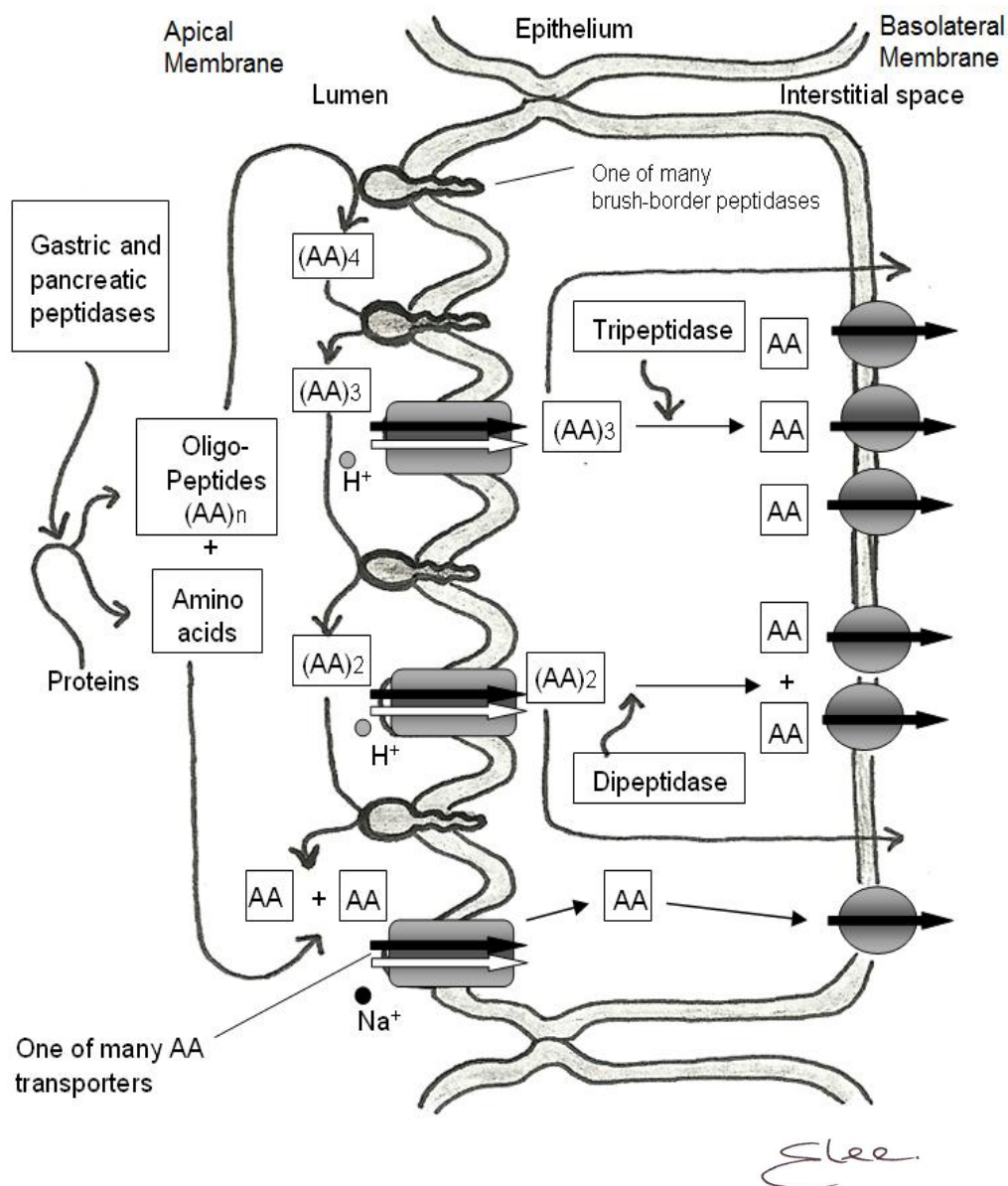
Major Amino Acid Transport Systems Detected in Intestinal Epithelial

Cells

Transport System	Substrates
➤ Brush Border (Apical) Membrane	
○ Neutral amino acids	
➤ NBB (SLC6A19)	Broad specificity for neutral amino acids
➤ PHE	Phenylalanine and methionine
➤ IMINO (SLC36A1)	Imino acids; proline, hydroxyproline
○ Basic amino acids	Lysine, cysteine, basic amino acids
○ Acidic amino acids	Glutamate, aspartate
➤ X-GA (SLC1A1)	
➤ Basolateral Membrane	
○ L	Broad selectivity
○ A	Broad selectivity
○ ASC (SLC1A5)	Neutral amino acids, alanine, serine, cysteine
○ N	Glutamine, histidine, asparagines

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ABSORPTION OF AMINO ACIDS



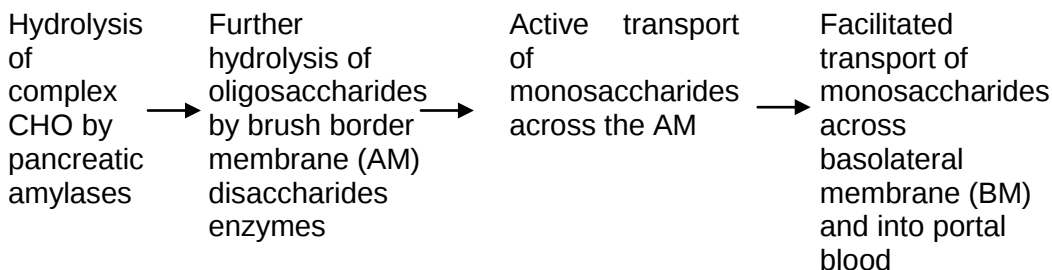
Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009, Figure 45-6, page 955.

Carbohydrate Assimilation

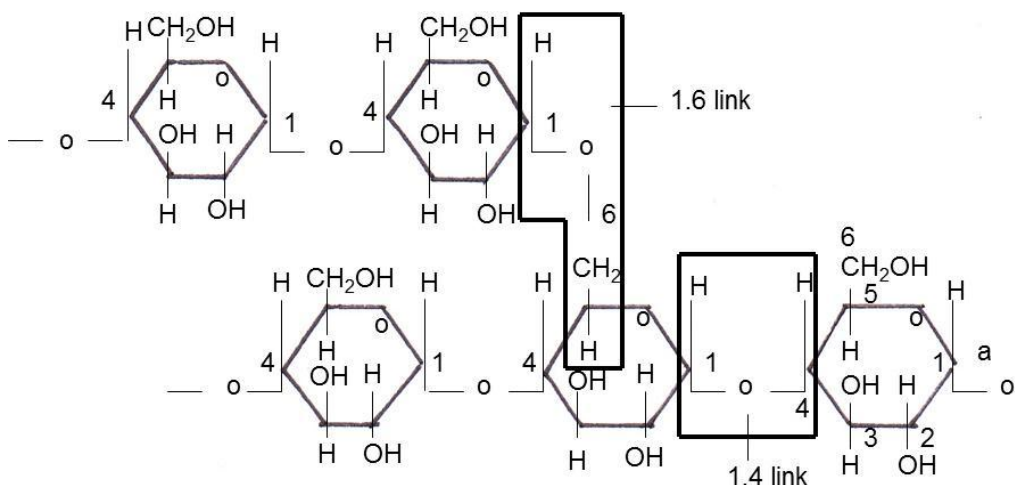
Source

- Ingested dietary disaccharides are split into monosaccharides by disaccharidases in the AM of the enterocyte..
- Carbohydrate polymers may be short (oligosaccharides) or long (polysaccharides).
- The polymers which cannot be digested are called non-digestible polymers, (aka “fiber”).
- Polymers which are digestible are broken down to monomers, such as the monosaccharides glucose, galactose and fructose.
- Pectins, cellulose and hemicellulose are both fiber and carbohydrates.
- Some dietary fibers such as lignins are not carbohydrates.
- Fiber may be soluble or insoluble. Some fiber can only be broken down by bacterial enzymes in the colon.
- The polysaccharide starch is a major dietary source of digestible carbohydrate.
- Starch is the storage form of carbohydrate in plants.
- Glycogen is the storage form of carbohydrate in animal tissue (“animal starch”).

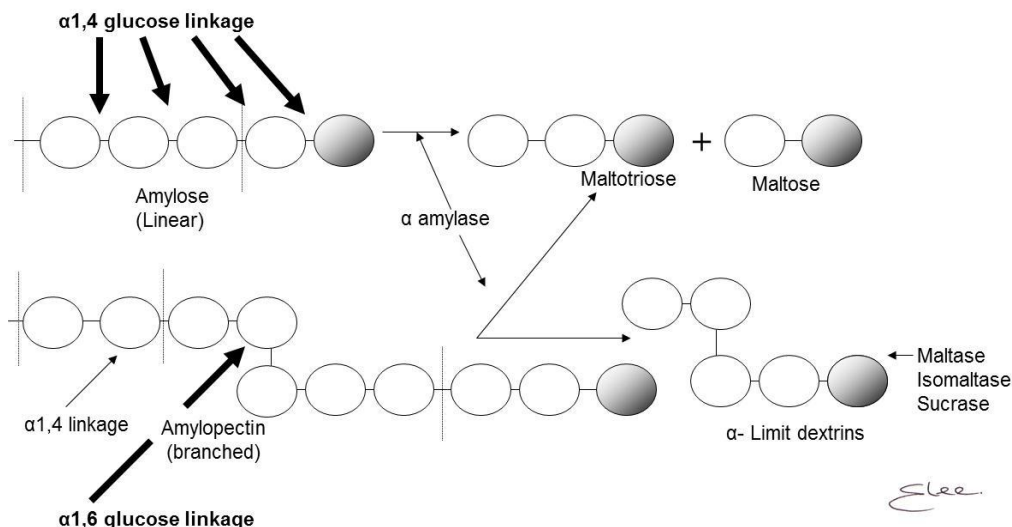
Small Intestinal in the Digestion and Absorption of Dietary Carbohydrate



STRUCTURE OF STARCH



HYDROLYSIS OF AMYLOSE AND AMYLOPECTIN



➤ Hydrolysis of complex carbohydrate by amylases

- The entire process of digestion and absorption of nutrients from the lumen, and across both the AM and BM, is known as “assimilation”.
- The initial digestion of nutrients in the mouth and stomach continues in the lumen of the upper small intestine, where it is furthered by the pancreatic and hepatobiliary secretions.

- The plant and animal starches contain the straight-chain polymer amylose, as well as the branch-chain amylopectin.
- In amylose, α -1,4 linkages join the glucose monosaccharides together to form the straight chain polymer.
- In amylopectin, there are α -1,4 linkages as well as α -1,6 linkages, which lead to the branching in this polymer.
- Amylopectins are more abundant than amylose, and there are more α -1,6 linkages in glycogens ("animal starch") than in plant starch.
- Salivary and pancreatic amylases in the intestinal lumen digest polymeric carbohydrates to disaccharides (intraluminal hydrolysis).
- Salivary and especially the pancreatic α -amylase hydrolyse only the internal α 1,4 linkage in starch.
- These amylases do not hydrolyse the terminal α -1,4 linkages, the α -1,6 linkages which form the branch points, or the α -1,4 linkages which are adjacent to the α -1,6 linkages.
- The products of the α -amylase are maltose (glucose-glucose, i.e., 2 glucose molecules), maltotriose (glucose-glucose-glucose, i.e., 3 glucose molecules), and α -limit dextrins (multiple glucose molecules which cannot be hydrolyzed by amylase because of their α -1,6 - linkages).
- Note that α -amylase does not hydrolyze the β -1,4 linkages in cellulose. This is why humans can't digest grass.
- Amylase produces maltose, maltotriose and α -limit dextrins, but no free glucose.

Brush border (apical) membrane (AM) hydrolysis of disaccharides, trisaccharide and α -limit dextrins

AM disaccharidase	Substrate and product
➤ Sucrase - isomaltase	○ Sucrose → glucose + fructose ○ Maltose → glucose ○ Terminal α – 1, 4 linkage of maltose and ○ α- limit dextrins → glucose

- Lactase
 - Lactose → glucose + galactose
- Maltase
 - Maltose, maltotriose → glucose
 - Terminal α – 1, 4 linkage of maltose, and
 - α - limit dextrins → glucose

Disaccharides → Monosaccharides

- The combined actions of maltase, isomaltase and sucrase yield glucose molecules from α -limit dextrins.
- Isomaltase is necessary to split the α -1, 6 link
- Digestion continues at the brush border (apical) membrane (AM) of the enterocytes.
- Disaccharides are present in the diet, and some of these are derived from the hydrolysis of oligosaccharides.
- The disaccharides also in the small intestinal AM hydrolyse the disaccharides to monosaccharides (membrane digestion).
- The milk disaccharide “lactose” is formed by the monosaccharides glucose and galactose.
- Lactase hydrolyzes lactose into galactose and glucose.
- The rate of hydrolysis (digestive activity) of lactase is low, so that the rate of hydrolysis of lactose limits the rate of absorption of its monosaccharides (galactose and glucose).
- In about 80% of humans, their AM lactase activity falls after weaning, and they cannot tolerate large amount of milk or milk products.
- These persons are said to be lactose-intolerant or “milk intolerant” or to have “primary lactase deficiency”.
- Most persons of Northern Western European ancestry (“Caucasians”) have persistently high levels of AM lactase, so they can enjoy drinking milk and dairy products into their adult years.
- When a Caucasian develops milk intolerance, it is usually due to a disease-related decline in AM lactase activity, such as from celiac disease.

- Fasting has little effect on the activity of lactase, but does reduce the activity of sucrase.
- Sucrose (“sugar”) is formed by the monosaccharides glucose and fructose.
- Sucrose is also formed from the action of maltase (aka glucoamylase) on the maltose and maltotriose derived from starch digestion.

➤ The AM

- Oligosaccharide side chains join the polypeptides of the hydrolytic enzymes which are then transferred to the Golgi apparatus.
- In the Golgi apparatus, there is further processing.
- After incorporation in the plasma membrane, luminal proteases cleave the molecule into its active subunits.
- Only a very small amount of dietary disaccharides are absorbed.
- The nascent polypeptide (N) of these AM digestive enzymes undergoes ribosomal mRNA translation, and then is translocated across the rough endoplasmic reticulum membrane (RER).
- The catalytic sites of AM sucrase-isomaltase, lactase and glucoamylase (maltase) project into the intestinal lumen, with the rest of the disaccharidase protein anchored in the AM.
- Sucrase-isomaltase hydrolyzes sucrose into fructose and glucose, as well as hydrolyzing some maltose into glucose.

- Maltase (glucoamylase) hydrolyzes maltose and maltotriose.
 - Sucrase-isomaltase and maltase also hydrolyze the terminal α -1,4 linkages of maltose and α -limit dextrins.
 - The rate of hydrolysis of sucrase is high, so that the rate of uptake of the sugars released by the hydrolyzing of the disaccharidases (fructose and glucose) is limited by the activity of the AM transporters, and not by the activity of sucrase.
 - The activity of the disaccharidases is higher in the proximal than in the distal small intestine, and is higher in the enterocytes in the upper as compared to the lower portions of the villus.
- Enterocyte Monosaccharide Transporters
- There are 3 enterocyte monosaccharide transporters.
 - SGLT₁, Na⁺ - dependent glucose/ galactose co-transporter in brush border (apical) membrane (AM)
 - GLUT₅, Na⁺ - independent fructose transporter in AM
 - GLUT₂, Na⁺ - independent monosaccharide transported in basolateral membrane (BM), which traffics from cytosol to AM in response to CHO-containing meal.
- SGLT₁
- Glucose and galactose are transported with Na⁺ by the Na⁺ - dependent transporter SGLT₁ in the enterocyte AM.
 - This is called secondary Na⁺ -dependent active transport, in which the hexose transport is energized by the Na⁺ electrochemical gradient caused by the BM Na⁺-K⁺ pump (Na⁺/K⁺ ATPase).
 - Water is absorbed in large amounts with the SGLT₁-transported monosaccharides glucose and galactose, as well as with the Na⁺ which is cotransported by SGLT₁ across the AM.
- GLUT5
- Fructose uptake across the AM is by Na⁺ - independent facilitated diffusion, using the transporter GLUT₅.

- Shortly after the oral intake of carbohydrates, GLUT₂ in the enterocyte cytosol trafficks from a cytosolic pool to and is inserted into the AM to facilitate further the uptake of glucose, galactose and fructose.
- Nutrients taken up across the AM may be further metabolized in the enterocytes.

➤ GLUT2

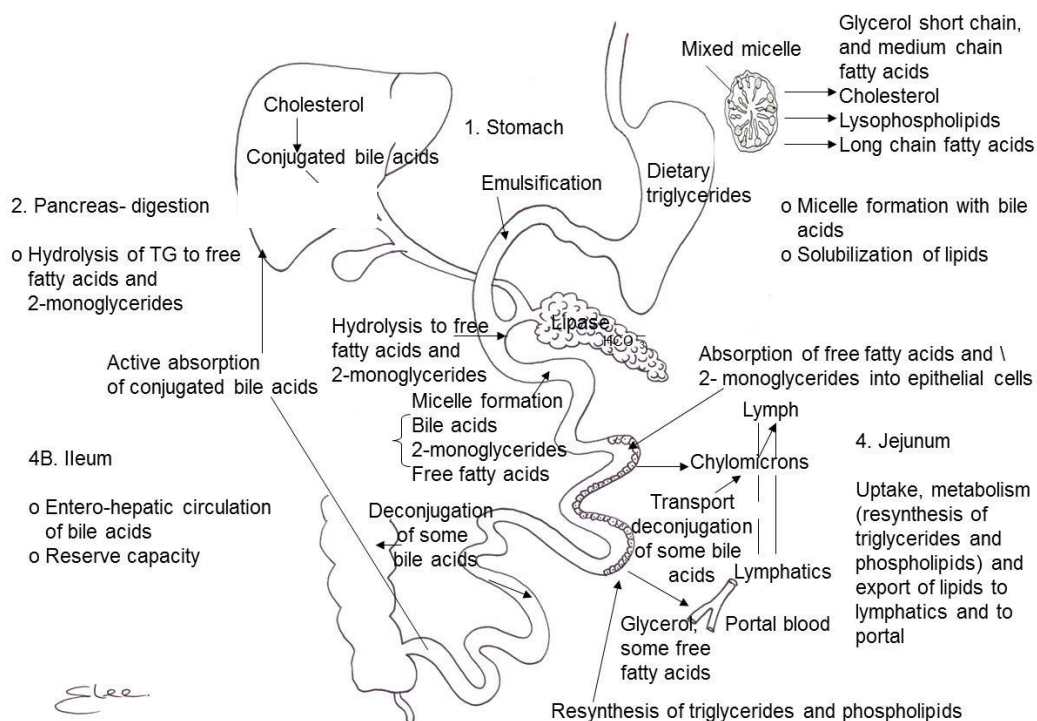
- GLUT₂ is Na⁺- Independent, and also facilitates the exit of those three monosaccharides across the BM and into the portal circulation.
- The activity of sucrase is increased when the dietary load of sucrase is increased.

• **Colonic Digestion and Absorption of Carbohydrates**

- The colon plays a role in the partial recovery of unabsorbed dietary carbohydrate (CHO) (intermediate and end products of anaerobic bacterial fermentation of carbohydrates).
- Bacterial fermentation of carbohydrates lead to increased bacterial production of hydrogen (H₂) gas, and this underlies the principle of the breath hydrogen test for small intestinal bacterial overgrowth (SIBO) or carbohydrate malabsorption.
- Undigested / unabsorbed colonic CHO is metabolized by bacteria to short chain fatty acids (SCFA).
- SCFA are absorbed into colonocytes, where they are used as the main fuel for these cells.
- An abnormal increase of CHO carbohydrate in the colon (such as from CHO malabsorption in the small intestine) leads to an excess of luminal SCFA, acidic stools, flatulence and bloating, and osmotic diarrhea.
- A test dose of carbohydrate may be labelled with ¹³C or ¹⁴C; malabsorption or SIBO leads to less absorption of labelled carbohydrate, less production of CO₂, and less ¹³C / ¹⁴C being detected in the breath.

Absorption of Triglycerides

DIGESTION AND ABSORPTION OF DIETARY TRIGLYCERIDES



Origin

- More than 90% of dietary fat is composed of TAGs (triacylglycerols, aka - triglycerides), which contain 3 fatty acyl esters (medium-or long-chain saturated or polyunsaturated fatty acids) of glycerol.
- Animal TAGs contain a low P/S ratio (polyunsaturated-to-saturated) of fatty acids, whereas there is high P/S ratio in vegetable TAGs.
- This bile content of lipid compares with 4-6 g/day of dietary phospholipids, 0.5 g/day of dietary cholesterol from animal cell membranes, and 70-100 g/day of dietary TAGs.

Emulsification

- Food preparation, chewing of lipids in the mouth and churning, of lipids in the stomach causes their of emulsification.

- Bile contains a rich source of endogenous lipids: 10-15 gm/day of lecithin (phosphatidylcholine), and 1-2 g/day of cholesterol (free, or unsaturated), plus 2-6 g/day of lipid from desquamated intestinal cells.
- The surface of the emulsion droplet is made up of multiple layers of monoacylglycerol, lysolecithins and other phospholipids as well as FAs.
- The surface monolayer of phospholipids, denatured protein, polysaccharides, and FAs prevents the small emulsion droplets from coalescing into large droplets.
- With emulsification of the lipid (mostly TAGs, DAGs [diglycerides], cholesterol esters [CEs], and non-polar lipids), small droplets are formed with a high ratio of droplet surface area to volume.
- This high surface area optimizes the potential for lipid digestive enzymes to perform their function.

Digestion

- Digestive lipases (gastric, milk, pancreatic) work on the oil-water interfaces of lipids.
- Gastric Lipase
 - In healthy infants, the activity of pancreatic lipase is low, and the infant relies on gastric lipase and human milk lipase to digest lipid in the diet.
 - In healthy adults, gastric lipases break down about 15% of dietary TAGs.
 - Gastric lipases are serine hydrolases with unique properties.
 - Are optimally active at a pH of 4
 - Are stable in the acid milieu of the stomach
 - Are not digested by gastric pepsin
 - Are not inhibited by the monolayer which covers the emulsified lipids
 - Gastric lipase removes the sm3-fatty acid from TAGs, leaving DAGs and FAs. The long-chain FAs hydrolyzed from TAG by the gastric lipase remain in the lipid droplets.

- Gastric lipase releases some FAs from dietary TAGs, and these FAs release cholecystokinin (CCK) and gastric inhibitory peptide (GIP) from the duodenal mucosa.
- Human milk lipase
 - The lipase in human milk is similar to the pancreatic carboxyl ester hydrolase.
 - Human milk lipase is not affected by acid or pepsin in the stomach.
 - Milk lipase is protected from proteolysis by bile salts.
 - When milk lipase enters the duodenum, it hydrolyzes TAGs, DAGs, MAGs, cholesterol esters, and fat-soluble vitamins.
 - Bile salts enhance the activity of milk lipase. For this reason, milk lipase is also known as bile-salt stimulated milk lipase.
 - Cholesterol ester hydrolase (CEH) (aka pancreatic esterase, cholesterol esterase, and lysophospholipase), acts on esterified cholesterol (CE) and MAG, to form free cholesterol and glycerol.
- Pancreatic lipase
 - The constituents of the monolayer arising from lipid digestion inhibit the activity of lipase.
 - The surface active protein and phospholipids displace lipase from the oil-water interface.
 - This displacement of lipase from the oil-water interface prevents the lipase access to the lipid droplet.
 - In turn this prevents the lipase to begin the next step in the lipid digestion process.
 - Pancreatic trypsin cleaves procolipase into lipase and enterostatin (a satiety factor).
 - CCK contracts the gallbladder and relaxes the sphincter of Oddi.
 - As a result, bile flows into the duodenal lumen.
 - CCK also stimulates the secretion of pancreatic enzymes including lipase, pro- colipase, cholesterol ester hydrolase and esterase.
 - Colipase and the pancreatic lipase form a complex.

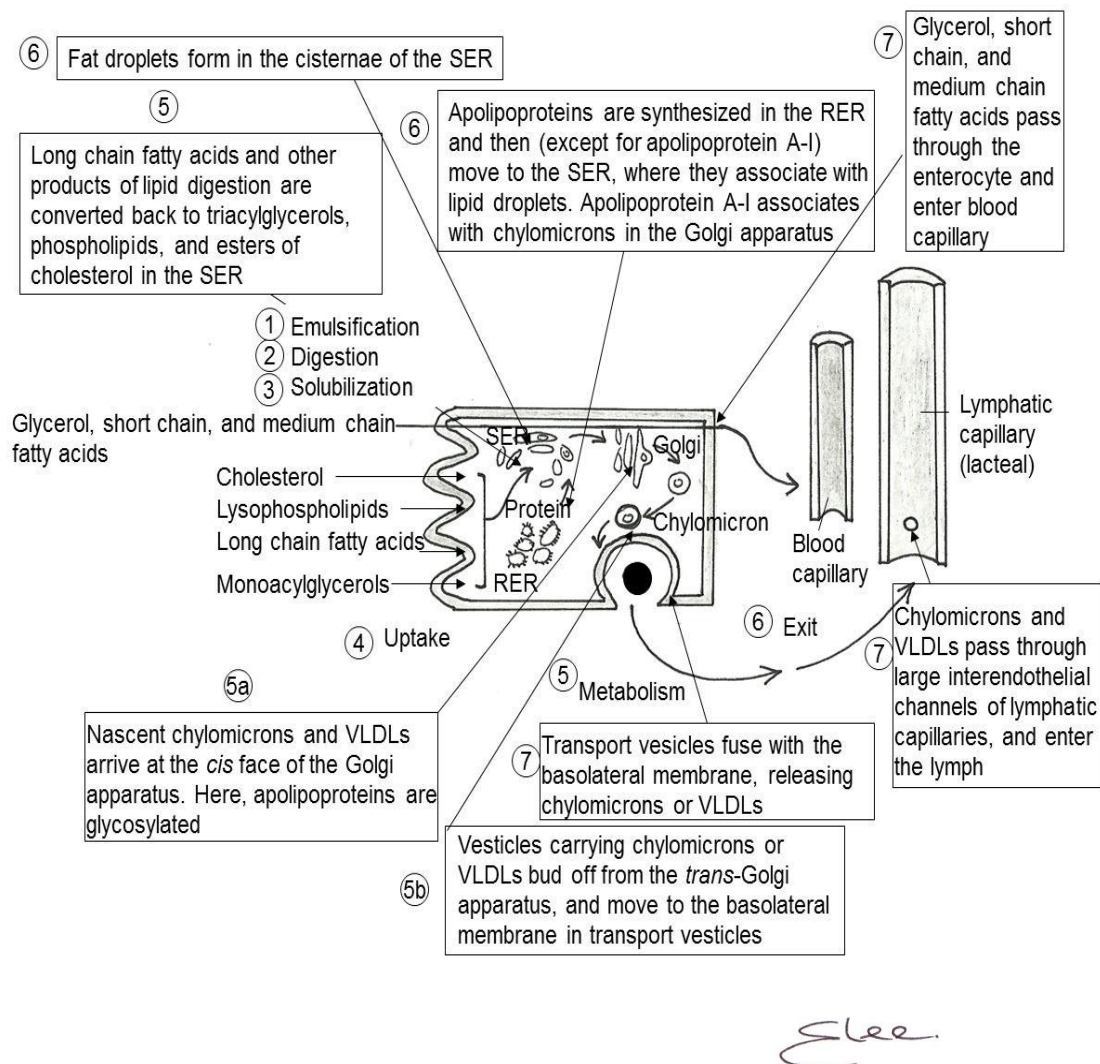
- The pancreatic lipase is adsorbed to the surface lipids, and it's the active hydrolytic sites cannot access the lipid (TAG) and begin digestion of lipid .
- When co-lipase is present, it displaces bile acids from the active hydrolytic sites of pancreatic lipase.
- The colipase causes a conformational change in the lipase, opening access to the hydrolytic site to the TAG, and hydrolysis of TAGs begin.
- The pancreatic lipase-mediated hydrolysis of TAGs removes FAs from the sm1 and sm3 positions.
- This leaves sm2- FAs and glycerol.
- PLA2 (phospholipase A2) from the pancreas or Paneth cells acts on glycersphospholipids to form lysophospholipids plus sm2-FAs.
- Bile salts activate PLA2, just as they activate milk lipase.
- The TAGs at or near the surface of the lipid emulsion droplet are broken down to MAGs and FAs.
- TAGs from the core of the emulsion droplet move towards the surface and continue the supply of substrate for hydrolysis by the pancreatic lipase.
- With digestion of the TAGs, more MAGs and FAs accumulate in the surface lipids.

Micellar solubilization

- A small portion of the surface lipids of the emulsion droplet form a multilamellar liquid-crystalline-micelle.
- In the presence of bile acids (BAs), several of the layers of lipid in the surface lipid coating are displaced, leaving a unilamellar vesicle.
- When a critical concentration of BSs is present in the intestinal lumen (known as the critical micellar concentration [CMC] about 5 mm), a negatively charged sphere of BSs forms.
- This sphere of BSs is called micelle.
- The surface lipids are still comprised of FAs, MAGs, PLs, cholesterol and bile salts.

- As more and more BSs are added, the unilamellar vesicles are transformed into negatively charged spheres, the bile acid micelles (BAM).
- The hydrophilic portion of the unilamellar bile acid vesicles face outwards, where they interface with the fluid contents of the intestinal lumen.
- The surface area-to-volume ratio of the vesicles becomes larger as the particles become smaller (emulsion droplet to multilamellar vesicle, multilamellar to unilamellar vesicle, unilamellar vesicles to mixed micelle).
- As the area-to-volume ratio of these vesicles increase, the rate of TAG hydrolysis becomes faster.
- If the CMC is not present in the intestinal lumen, lipid malabsorption results.
- Adjacent to the brush border membrane (aka apical membrane [AM]) of the enterocytes in the upper small intestine, there is a layer of poorly stirred water, the unstirred water layer (UWL).
- The UWL has dimensions of thickness, surface area and viscosity (from secreted mucus).
- The diffusion coefficient of solutes through the UWL diffusion barrier is slower than in the bulk phase of the liquid in the intestinal lumen.
- In the small intestine, the UWL creates an acid microenvironment between the alkaline contents in the lumen, and the AM (in the stomach, the UWL creates an alkaline microenvironment).
- The bile BSM contains several forms of lipids, and is known as a mixed micelle.
- When the CMC is present in the lumen, lipids are solubilized and can be absorbed.
- The hydrophobic portions of the lipids in the mixed micelle face inwards towards the core.

Enterocyte AM uptake, metabolism and BM exit of lipids

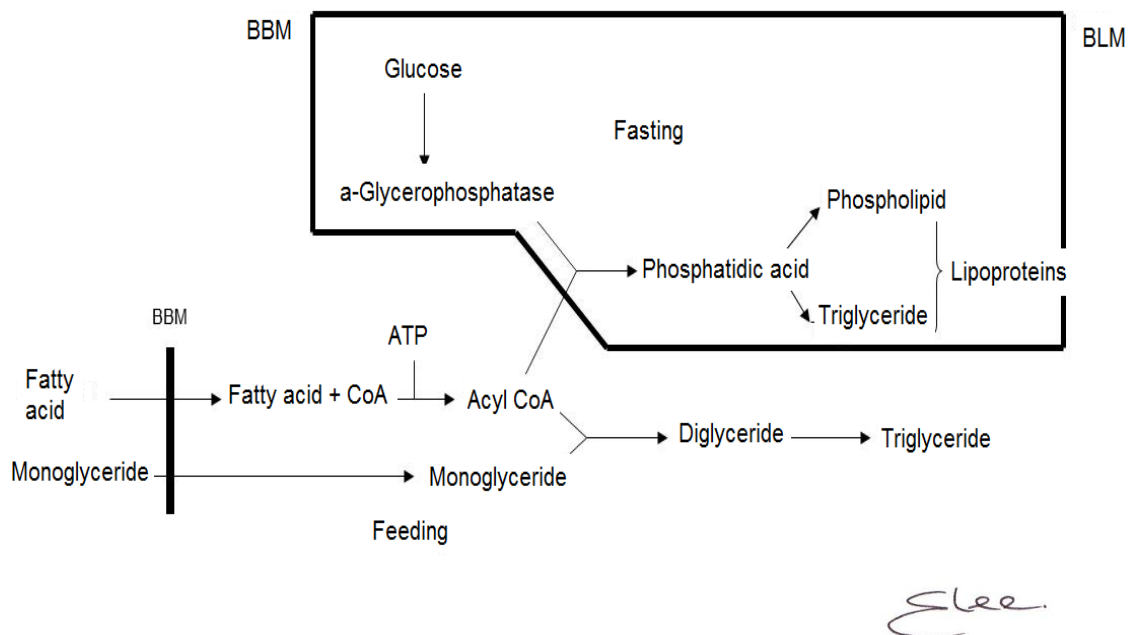


Adapted from: *Medical Physiology*, Figure 45-14, page 967, Second Edition, 2009

Brush Border (Apical) Membrane (AM) uptake

- The bile acid micelle (BAM) slowly diffuses across the UWL, and acts as a reservoir for the high concentration of lipids.
 - Cholesterol, lysophospholipids, long chain fatty acids, monoacylglycerol, presented to the AM of the enterocyte.
 - Once the BAM reaches the AM, these lipophilic lipids in the BAM may move either directly into the highly lipophilic AM, or may partition from the BAM into a liquid phase and then be transported across the AM.
 - Extracellular LCFA may bind directly to a fatty acid transport protein (FATP) dimer complex in the AM, and be transported into the enterocyte.
 - Alternatively, LCFA may bind first to CD36, which transfers the LCFA to FATP dimer.
 - Cholesterol in the BAM is free cholesterol (CH), i.e. non-esterified cholesterol.
 - The facilitated transport of CH across the AM is by the transporter (carrier) protein NPC1L1 (Nieman-Pick-C-I-like-I).
 - When the BAM is depleted of its solubilized lipid products, the bile acids (BA) return to the intestinal lumen when they solubilize more lipids for absorption, pass towards the distal small intestine.
- **Enterocyte Cytosolic Metabolism of Absorbed Fatty Acids and Monoglycerides**
- Once the lipophilic lipids such as long-chain fatty acids [LCFAs], monoacylglycerols [MAGs], lysophospholipids and cholesterol are absorbed, there is a complex series of intracellular metabolic steps.
 - In the enterocyte cytosol, there are numerous lipid fatty acid binding proteins (FABPs) which lower the cytosolic concentration of FAs, and carry lipids to the SER (smooth endoplasmic reticulum).
 - In the SER, the products of lipid digestion which have crossed the AM are metabolized back to the more lipophilic TAGs, CEs (cholesterol esters) and phospholipids.

Metabolic fate of absorbed fatty acid and monoglyceride in enterocytes



Abbreviations: AM, apical (brush border) membrane; BM, basolateral membrane

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-6, page 1704, Ninth Edition, 2010

- These lipophilic products of digestion form lipid droplets in the cisternae of the SER.
- After a meal, the large amounts of MAGs and FAs, which entered the enterocyte through the AM, are re-esterified by the MAG-pathway.
- During fasting, FAs entering the enterocyte across the BM are re-esterified by the phosphatidic acid pathway.
- This phosphatidic acid in the enterocyte is derived from G-3-P (glycerol-3-phosphate, produced from glucose and amino acids, or from the breakdown of biliary lecithin).
- Acetyl CoA synthetase activates especially the LCFAs to be used in both the MAG and the phosphatidic acid pathways.

- Intracellular LCFAs are coupled to coenzyme A (CoA) by long-chain fatty acyl-CoA synthetase (LACS), preventing their efflux, cytoplasmic fatty acid binding protein (FABP) acts as a buffer for LCFA.
- The proteins which are secreted by the enterocyte RER are called “apolipoproteins” (or apoproteins).
- The apolipoproteins bind to the TAGs and CEs.
- Some apolipoproteins are secreted only in enterocytes.
- Apolipoproteins, synthesized in the rough endoplasmic reticulum (RER), assist in the formation of chylomicrons and very-low-density lipoproteins (VLDL) in the tubular endoplasmic reticulum and Golgi apparatus.
- These apolipoproteins traffic to the SER, where they associate with lipid droplets..
- At the *cis* face of the golgi, apolipoproteins (very low density lipoproteins) arrive at the *cis* face of the Golgi apparatus, are glycosylated, containing the nascent chylomicron and VLDL.
- Apolipoproteins A-1 from the RER associated with chylomicrons do not traffic to the SER, but instead go directly to the Golgi.
- The chylomicrons and the VLDLs contain the same apolipoproteins.
- The chylomicrons are larger (~250 nm) than the VLDLs (30-80 nm).
- Chylomicrons contain mostly exogenous (dietary lipids), whereas the VLDLs contain mostly endogenous lipids.
- The vesicles which carry chylomicrons or VLDLs bud off from the *trans*- Golgi apparatus, forming transport vesicles.
- These vesicles carrying chylomicrons and VLDL diffuse to the BM, from which they are released into the lymphatics.

Transport across BM

- The transport vesicles traffic to the BM, releasing their chylomicron and VLDLs by the process of exocytosis.
- Glycerol, as well as short- and medium- chain length fatty acids avoid the apolipoproteins, transport vesicles, and lymphatics. And pass directly from the enterocyte cytosol, across BM, and into the portal circulation.
- The wall of the lymphatics is highly permeable due to large fenestrations in its endothelial wall.
- The chylomicrons and the VLDLs readily cross through the fenestrations and into the lymphatic circulation.

Please refer to the Chapter on the Liver, for details of the hepatic portion of this complex process.

Absorption of fat soluble Vitamins A, D, E, and K

- Gastric acid and proteolysis releases the esterified fat soluble (FS) vitamins from their associated proteins.
- The free form of the FS vitamins is formed from dietary esters by the action of the carboxyl ester hydrolases in pancreatic juice and in the AM of the enterocytes.
- The assimilation of the fat soluble (FS) vitamins A, D, E, and K, generally follows that of the other lipids. Gastric HCl, and proteolysis releases the esterified FS vitamins from their associated proteins.

Cholesterol

➤ Overview

- The cholesterol assimilation (digestion and absorption) is similar to TAGs.
- Cholesterol in the diet is in the form of esters.
- Cholesterol esters are hydrolysed by pancreatic cholesterol esterase.

- Cholesterol solubilized in the BAMs diffuses across the UWL.
- At the AM, cholesterol partitions from the BAM and is absorbed passively through AM.
- Cholesterol is also transported into the enterocyte cytosol by way of the cholesterol transporter (NPC1L1 [Niemann-Pick-C-I-like]).
- Digestion and absorption
 - Dietary and secretory cholesterol are in the ester form, and the free cholesterol must just be de-esterified to free cholesterol by pancreatic cholesterol ester hydrolase (CEH).
 - The free cholesterol is solubilized in bile salt micelles with TAGs and PLs (phospholipids); forming mixed micelles.
 - The mixed micelles diffuse across the intestinal water layer (IWL), and up close to the BBM (brush border membrane) of the enterocyte).
 - The lipid constituents partition from the mixed micelle and cross the apical membrane (AM) of the enterocytes, by passive diffusion through the lipid bilayer of the AM, as well as by transport proteins. The AM transporter for cholesterol is NPC1L1 (the Niemann – Pick C1 like transporter protein).
- Enterocyte cytosole
 - Once the free cholesterol is in the enterocyte, it is esterified by ACAT (acyl CoA ester cholesterol transferase), in the endoplasmic reticulum.
 - Esterified cholesterol is solubilized by binding to apoprotein.
 - The enterocytes synthesize apoprotein I and II (A-I and A-II).
 - A-I and A-II are part of the apoproteins forming chylomicrons in the enterocyte.
 - The apolipoproteins pass to Golgi apparatus, where they are glycosylated.

- In the enterocyte, and more so in the hepatocyte, cholesterol is synthesized.
- The chylomicrons remnants in the fed state and VLDLs pass through large interendothelial channels of lymphatic capillaries, and enter the lymph fluid in the lymphatic system.
- The ATP-binding cassette (ABC) transporter, ABCA1 translocates cholesterol, and phospholipids (PLs) to the BM.
- The cholesterol and PLs form lipid domains that interact with amphipathic α -helices in apolipoproteins.
- The enterocytes (like the liver) contain HMG-co-reductase, and also synthesize cholesterol.

➤ Small Intestinal “Secretion” of Cholesterol

- Enterocytes absorb, metabolize and export dietary (exogenous) as well as secreted (endogenous) lipids.
- Dietary triacylglycerol (TAG, aka triglycerides) and cholesterol are exported across the enterocyte basolateral membrane (BM) as chylomicrons.
- Chylomicrons are 80% to 90% TAG, plus cholesterol, phospholipids, and apoproteins are secreted by the enterocyte, passing through the BM.
- Chylomicrons pass from the BM to lymphatics, to the thoracic duct, and into the systemic circulation.
- The TAG in chylomicrons are partially broken down by lipoprotein lipase (LPL).
- LPL is present in the walls of the capillaries in muscle and adipose tissue.
- The glycerol and fatty acids are digested and leave the chylomicrons. which now contain just cholesterol.
- These cholesterol-enriched chylomicrons are called remnant chylomicrons.

- The remnant chylomicrons contain small amounts of DAG, and large amounts of cholesterol.
 - The remnant chylomicrons pass in the systemic circulation to the liver.
 - The digestion of VLDL by LDL yields cholesterol (and phospholipid) from the surface of the VLDLs.
 - This VLDL-derived cholesterol leaves the non-hepatic tissue by the cholesterol efflux transporter (CET), ABCA1.
 - This cholesterol binds to HDL (high density lipoproteins).
 - This free cholesterol plus the phospholipid lecithin, are acted upon by the enzyme LCAT cholesterol acyltransferase.
 - The LCAT forms cholesterol esters plus lysolecithin from the free cholesterol and lecithin.
 - The HDL is now enriched with cholesterol esters (CE).
 - HDL-CE binds to SR-B1 (scavenger receptor class B type 1) on the hepatocyte.
 - SR-B1 leads to the uptake of HDL-CE (this is not a process of endocytosis).
 - HDL-CE may also transfer its CE to VLDL, IDL and LDL.
 - This transfer of HDL-CE occurs through the action of CETP (cholesterol ester transfer protein).
 - Thus HDL removes cholesterol from peripheral tissues by
 - SR-B1, and
 - CETP
 - This removal of cholesterol from peripheral tissues by SR-B1 and CETP, and the eventual excretion of cholesterol in bile is called reverse cholesterol transport.
- Role of hepatic sinusoidal membrane in cholesterol metabolism

- The chylomicron and VLDL cross the sinusoidal membrane (SM) of the hepatocyte and mix with, the absorbed cholesterol synthesized de novo through the action of HMG CoA reductase.
- The same steps are followed for the association with apoproteins, glycosylation of apolipoproteins, the budding off of chylomicrons and VLDL from the Golgi apparatus, and the transport of the chylomicrons across the CM of the hepatocyte and into the bile.
- The hepatic uptake of cholesterol is mediated by three proteins: the low-density lipoprotein (LDL) receptor (LDLR) for LDL, by scavenger receptor class B type I (SR-BI) for high-density lipoprotein (HDL), and by the chylomicron remnant receptor (CMRR) for chylomicron remnants (CMR).
- The remnant chylomicrons bind in the liver to the sinusoidal membrane (SM) receptors
 - LDL-related receptor, and
 - LDL-receptor (low-density lipoprotein)
- Enterocytes absorb, metabolize and export dietary (exogenous) as well as secreted (endogenous) lipids.
- Dietary triacylglycerol (TAG, aka triglycerides) and cholesterol are exported across the enterocyte basolateral membrane (BM) as chylomicrons.
- Chylomicrons are 80% to 90% TAG, plus cholesterol, phospholipids, and apoproteins are secreted by the enterocyte, passing through the BM.
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- The glycerol and fatty acids are digested and leave the chylomicrons. which now contain just cholesterol.

- These cholesterol-enriched chylomicrons are called remnant chylomicrons.
- The remnant chylomicrons contain small amounts of DAG, and large amounts of cholesterol.
- The remnant chylomicrons pass in the systemic circulation to the liver.
- The remnant chylomicrons bound to the LDL- and LDL-related receptors enter the hepatocyte by receptor-mediated endocytosis.
- In the hepatocyte, lysosomes break down to remnant chylomicrons.
- The TAG broken down by LPL contains certain long-chain fatty acids (LCFA) which are taken up only by the liver.
- These LCFA cross the SM of the hepatocyte by facilitated uptake as well as “flip-flow” across the membrane.
- Cholesterol delivered to the liver in chylomicron remnants join cholesterol passing into hepatocyte in LDL.
- LDLs are the major carrier of the cholesterol in the blood.
- Blood LDLs are taken up into the hepatocytes by endocytosis.
- The liver also synthesizes cholesterol de novo from acetyl CoA and mevalonate.
- Some cholesterol is used for the synthesis of bile salts (BSs) via the “neutral” pathway.
- Some cholesterol is used for the synthesis of bile salts via the “acidic” pathway.
- The chylomicron and VLDL pass through the intestinal lymphatic, and in the portal circulation.
- The small amount of TAG delivered to the hepatocytes in the remnant chylomicrons undergoes breakdown into glycerol and fatty acids (FAs).

- The fatty acids in the liver undergo metabolism, by β -oxidation, to Acetyl CoA, or they are used to reform TAG.
- Acetyl CoA may be used for
 - Entry into the citric acid cycle to produce energy
 - Production of acetoacetate, to be used for energy not by the liver but instead by the brain, kidney, and muscle.
 - Production of ketone bodies (acetoacetate, acetone and β -hydroxybutyrate) which may accumulate in excess during fasting or diabetic ketoacidosis.
- The hepatic TAG re-esterified with glycerol to TAG are bound to lipoprotein, forming VLDL (very low density lipoprotein).
- VLDL may be stored in the liver, or exported from the liver for use by the peripheral tissue, where the VLDL are broken down by LDL.
- In the fasting state, VLDL shuttle endogenous TAG to muscle and adipose tissue, whereas chylomicrons are important in the fed state.
- The enzyme HMG-CoA reductase is in the membrane of the ER (endoplasmic reticulum) of the hepatocyte.
- The activity of HMG-CoA reductase is increased by
 - ↓ cell cholesterol
 - ↓ cell mevalonate
 - ↑ cell demand for metabolites derived from mevalonate
 - ↑ gene translation
 - Depletion of the bile acid pool
- This upregulation occurs by the process of
 - ↑ stability HMG-CoA reductase.
- The activity of HMG-CoA reductase is reduced by fasting, high levels of cholesterol in cells, and sterol acting on sterol regulatory elements (SRE) and sterol regulatory element binding proteins (SREBPs).
- At the Golgi apparatus the apolipoproteins are glycosylated.

- The lipid is digested, absorbed and metabolised in the enterocyte (please see section on lipid absorption in the chapter small intestine)

CLINICAL PHYSIOLOGICAL CHALLENGE – Control of Cholesterol Metabolism

Case: A 45 year old woman with primary biliary cirrhosis (PBC) has hypercholesterolemia and xanthelasma.

Questions: Outline the role of the liver in maintaining normal concentrations of cholesterol in the blood.

➤ Hepatic cholesterol balance

- Free cholesterol is derived from intracellular synthesis, and from the uptake of chylomicron remnants and lipoprotein from the circulation.
- Some cholesterol is stored as cholesterol ester: ACAT (acyl CoA – cholesterol ester transferase, esterifies free cholesterol to fatty acids)
- CEH (cholesteryl ester hydrolase hydrolyses the ester linkage).
- Bile acids are synthesized from free cholesterol, and both are secreted into bile.
- 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is the rate-limiting step for the synthesis of cholesterol.

➤ Hepatic excretion of cholesterol across the canalicular membrane (CM)

- The apoproteins (except for apolipoprotein [A-I] traffic to the SER, where they associate with lipid droplets.
- Apolipoproteins solubilize cholesterol and phospholipids, and generate nascent HDL particles.
- This interaction solubilizes the lipids and generates nascent HDL.
- The nascent HDL particles dissociate from the cell.
- Nascent chylomicrons and VLDLs (very low density lipoproteins) arrive at the cis face of the Golgi apparatus.

- Some cholesterol is used for the formation of very-low-density lipoprotein (VLDL), which is secreted into the portal blood.
- Apolipoprotein A-I is associated with chylomicrons in the Golgi apparatus.
- The vesicles which carry chylomicrons or VLDLs bud off from the trans- Golgi apparatus, forming transparent vesicles.
- The transport vesicles traffic to the BM, releasing their chylomicron or VLDLs by exocytosis.
- Glycerol, short chain, and medium chain fatty acids pass through the enterocyte, across the BM, and enter blood capillary.
- These products avoid the apolipoproteins, transport vesicles, and lymphatics.
- The synthesis is regulated by two rate-limiting enzymes cholesterol 7 α -hydroxylase (CYP7A1), the “neutral pathway”, and sterol 27-hydroxylase (CYP27A1), the “acidic” pathways.
- The HDL particles leave the hepatocyte.
- Cholesterol (Chol), bile salts (BS), and phospholipids (PL) are secreted across the canalicular membrane by the three lipid transporters ABCG5/G8, ABC B11, and ABCB4, respectively.

Bile Acids – Intestinal Components of Enterohepatic Circulation (EHC) of Bile Acids (for ease of studying and review, this section has been repeated)

Duodenum and Jejunum

- Only small amounts of BAs are absorbed by passive diffusion along the length of the small intestine.
- The bile passes through the extrahepatic biliary tree, after about half of the hepatic bile has become concentrated by water absorption in the gallbladder.

- This mixture of hepatic and gallbladder bile enters the duodenum, where the bile acids solubilize lipids and continue the process of lipid absorption.
- The concentration of BAs which is required to form the micelle is known as the “critical micellar concentration” (CMC).
- The enterohepatic circulation of bile salts (EHC) functions to maintain the CMC in the lumen of the proximal intestine, and thereby facilitate the absorption of lipids.
- Only small amounts of bile acid are absorbed by diffusion in the jejunum.
- Non-ionic diffusion of the protonated unconjugated bile acids (H - BA) is much higher than is ionic (BA⁻)diffusion.
- This low absorption of bile provides the means to continue to have sufficient bile acids in the lumen to solubilize and to facilitate the absorption of about 95% exogenous and endogenous lipids.
- The complex and integrated process of lipid absorption is considered in a later section; here we only briefly consider lipid absorption against the overall perspective of understanding the enterohepatic circulation of bile acids.
- Once the concentration of bile in the duodenal lumen reaches a critical concentration (about 5 mM), the bile acid monomers form micelles.
- This critical concentration of bile acids is called the “critical micellar concentration” (CMC).
- When the CMC is reached, the negatively charged spheres (“micelles”) are formed.
- These simple micelles solubilize the lipid digestive products in the intestinal lumen (fatty acids, B-glycerol, phospholipids, free cholesterol).
- These micelles that have solubilized the lipid digestive products are called mixed micelles (MM).

- MM diffuse across the unstirred water layer on the luminal side of the enterocyte brush border (apical) membrane (AM).
- In the aqueous phase in the intestinal lumen, the water-soluble lipids, glycerol, as well as short- and medium- chain length fatty acids diffuse across the AM, through the cytosol of the enterocyte, and across the BM into the portal circulation
- Some of the lipids solubilized in the MM partition into the AM, and diffuse into the cytosol of the enterocyte.
- Some fatty acids are transported across the AM, by FAT.
- The EHC also provides a pathway for the secretion of cholesterol from the body, by way of the metabolism of CH to BAs.
- Cholesterol is transported across the AM by the Niemann-Pick C1 like1 protein transporter (NPC1L1).
- When the MM are depleted of their solubilized lipids, the now simple micelles move back into intestinal lumen where they solubilize more lipids, and once again shuttle across the UWL and AM.

Intestinal Lumen

- The content of bacteria in the intestinal lumen increases from the proximal to the distal small intestine (10^4 to $\sim 10^7$ per hpf [high power field]).
- Bacteria in the terminal ileum and colon deconjugate bile salts (BA-Z) to form bile acids (H-BA).
- Bacteria also dehydroxylate the primary bile acids secreted by liver (cholic and chenich acids, forming the secondary bile acids deoxycholic and lithcholic, respectively.
- The secondary bile acids may be dehydroxylated again by intestinal bacteria into the tertiary bile acids.
- The tertiary bile acids may be absorbed and enter the enterohepatocyte circulation together with the primary and secondary bile acids.

- In the terminal ileum and colon, bacteria deconjugate a small amount of these bile salts to form unconjugated bile acids ($\text{H} \cdot \text{BA} \leftrightarrow \text{H}^+ + \text{BA}^-$), thereby allowing $\text{H} \cdot \text{BA}$.
- This deconjugation by luminal bacteria allows the conjugated bile acids ($\text{H} \cdot \text{BA}$) to be passively absorbed by non-ionic diffusion.
- Secondary metabolism of bile acids by the intestinal bacteria microbiota includes
 - 7 α -dehydroxylation
 - Deconjugation
 - Epimerization of 3 α - and 7 α - hydroxyl groups
 - Hepatic reduction of the 7-oxo derivative of chenodeoxycholic acid to 7-oxo lithocolic acid
 - Hepatic re-epimerization of 3 β -hydroxy bile acids
 - Sulfation at the 3 or 7 positions by the liver and kidney
- Like the unconjugated primary bile acids, the unconjugated secondary bile acids are absorbed in the ileum, pass in the portal blood to the hepatocyte sinusoidal membrane, where they are taken up by the hepatocytes and reconstituted in the hepatocyte cytosol.

Ileum

- Once the lipids have been absorbed, the bile acids pass along the length of the jejunum to the ileum.
- The bile salts (BA-Z) are efficiently reabsorbed by ASBT, then active uptake by ileal ASBT (Na^+ /bile transporter) is low.
- Conjugated bile acids are actively transported across the ileocyte AM as conjugated bile acids (BA-Z) by ASBT (apical sodium bile acid transporter; (gene symbol, SLC10A2).
- Bile acids in the cytosol of the ileocytes are actively transported across the BM by BSEP (bile salt export protein; gene symbol ABC B11).
- The unconjugated primary, secondary and tertiary bile acids are also cycled in the portal circulation back to the liver.

- The bile acids which are not absorbed by the small intestine pass into the colon.
- The usual loss of unabsorbed bile acids in the feces (about 600 mg per day) is matched by hepatic synthesis of bile acids.
- The BAs which are taken by the hepatocyte sinusoidal membrane (SM) mix with any newly synthesized BAs.
- The BAs traffic to the canalicular membrane (CM) of the hepatocyte where they are transported into the bile ducts back into the duodenal lumen, to form BAMs.

Portal Blood and Hepatocyte Sinusoidal Membrane (SM)

- These bile acids return to the liver through the portal blood, and are taken up by the sinusoidal membrane (SM) of the hepatocyte.
- The bile acids cycle in the EHC (liver-intestine and back to the liver) numerous times (4 to 6) with each meal.
- Because the intestinal absorption of bile acids is so high, the EHC is very efficient, and the liver does not need to produce large amounts of bile acids each day.

Control of the Enterohepatic Circulation (EHC) of Bile Acids

Overview

- ↓ BA uptake (ASBT) - ↓ BA in ileocyte cytosol - ↓ FXR - ↓ FGF19 - ↓ FGF4 / B-klotho - ↓ transcriptional repressor on 7 α -hydroxylase - ↑ conversion of cholesterol → 1° BA
- Transcriptional regulator of the nuclear bile acid receptor:
 - 1° BA are synthesized by the hepatocytes
 - 1° BA increase FXR
 - FGF 19 passes to the liver in the portal venous blood.
 - FGF 19 interacts with the dimeric receptor FGFR4/ β -klotho present on the SM of the hepatocyte.
 - The activated FGFR4/ β -klotho receptor initiates a phosphorylation cascade.

- This phosphorylation cascade causes transcriptional repression of the gene which encodes cholesterol 7 α -hydroxylase, the rate-limiting enzyme in bile acid biosynthesis.
 - ↓ hepatic cholesterol 7 α -hydroxylase, ↓ 1° BA are synthesized in the hepatocytes.
 - ↓ ASBT in the ileal AM, decreasing bile acid absorption into the ileocytes.
 - ↑ BSEP, so ↑ BA is transported out of the ileocytes.
 - ↓ NTCP, thereby decreasing the uptake of conjugated (BA-Z) and unconjugated bile salts (BA) into the hepatocytes across the CM.
- In patients with ileal dysfunction or resection, there will be ↓ absorption of the bile acids across the AM of the ileal enterocytes.
 - When the concentration of bile acids in the ileal enterocyte is lower, and there will be ↓FXR and ↓FGF 19 formation and release.
 - ↓ FGF 19 means ↓ hepatic activation of FGFR4/ β -klotho.
 - For unknown reasons, FGF 19 release from the ileal enterocyte is impaired, leading to increased hepatic bile acid biosynthesis.
 - The bile acids in the ileal enterocyte activate FXR, the nuclear receptor for bile acids.
 - BA ileocyte AM uptake
 - ↑FXR
 - ↑ KLB signalling
 - ↓ BA synthesis in hepatocyte
 - ↓ NTCP in hepatic SM
 - When the concentration of bile acids in the ileocyte is low (such as from ↓ uptake) FGF19 is not released.
 - Low level of bile acids and low release of FGF19 leads to low levels of FGFR4/ β -klotho activity on the hepatocyte membrane.

- Low FGF19 and FGFR4/ β -klotho removes the inhibition of 7 α -hydroxylase leads to increased conversion of cholesterol to bile acids.
- If there is only mild loss of ileal absorption capacity, such as from resection of less than 100 cm of the terminal ileum (as would often be done in persons with Crohn's disease), there will only be a small decrease of FGF 19, FGFR4/ β -klotho, there will be enhanced activity of 7 α -hydroxylase which may be sufficient to increase primary bile acid synthesis enough so that critical micellar concentration of bile acids is maintained, so that fat malabsorption would not occur.

Disease Correlates

- With the < 100 cm of resection, there will be sufficient ileal malabsorption of bile acids in the ileum that an excess of bile salts will spill into the ileum, stimulate cAMP in the colonocytes, and cause a secretory bile salt-induced diarrhea (choleretic enteropathy).
- With a major ileal resection (> 100 cm of terminal ileum), the capacity of the 7 α -hydroxylase enzyme to be upregulated is exceeded, and not enough primary bile acids can be produced to maintain the upper intestinal luminal bile acid concentration above the CMC.
- Defective FGF19 release from the ileum is reported in patients with IBS-D whose symptoms improve with the BA sequestrant cholestyramine, suggesting that excessive hepatic BA synthesis due to defective FGF19 signalling is associated with BA diarrhea.
- In patients with idiopathic bile acid malabsorption, ileal bile acid transport is normal.

CLINICAL PHYSIOLOGICAL CORRELATION – Bile Acid Wastage

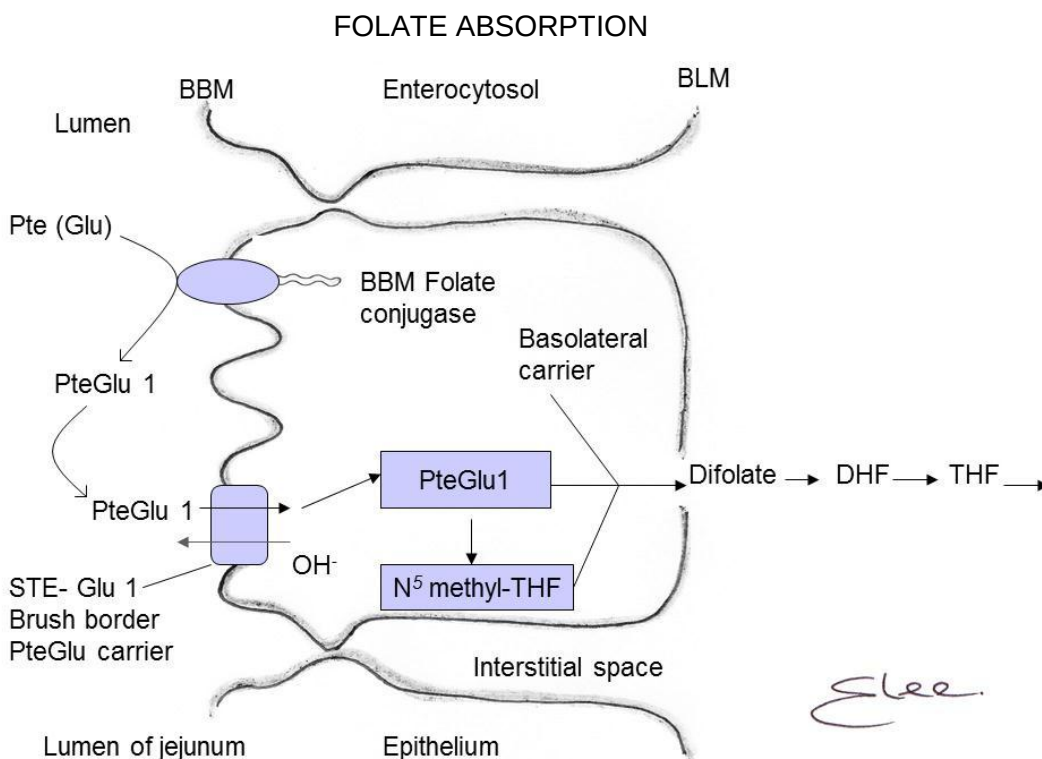
Background: When a person undergoes an ileal resection of < 100 cm, the liver attempts to upregulate the synthesis of primary bile acids from cholesterol in an attempt to maintain a normal proximal intestinal concentration of bile acids, and thereby maintain normal fat absorption.

Problem: Explain the effect of reduced ileal uptake of bile acids on the mechanisms controlling the hepatic synthesis of bile acids. Explain the rationale for a short ileal resection (< 100 cm) causing choleraic diarrhea, whereas a longer ileal resection (> 100 cm) results in steatorrhea.

Water Soluble Vitamins

Folic Acid

- THF is essential for the synthesis of DNA.



Abbreviations: AM, brush border (apical) membrane; BM, basolateral membrane

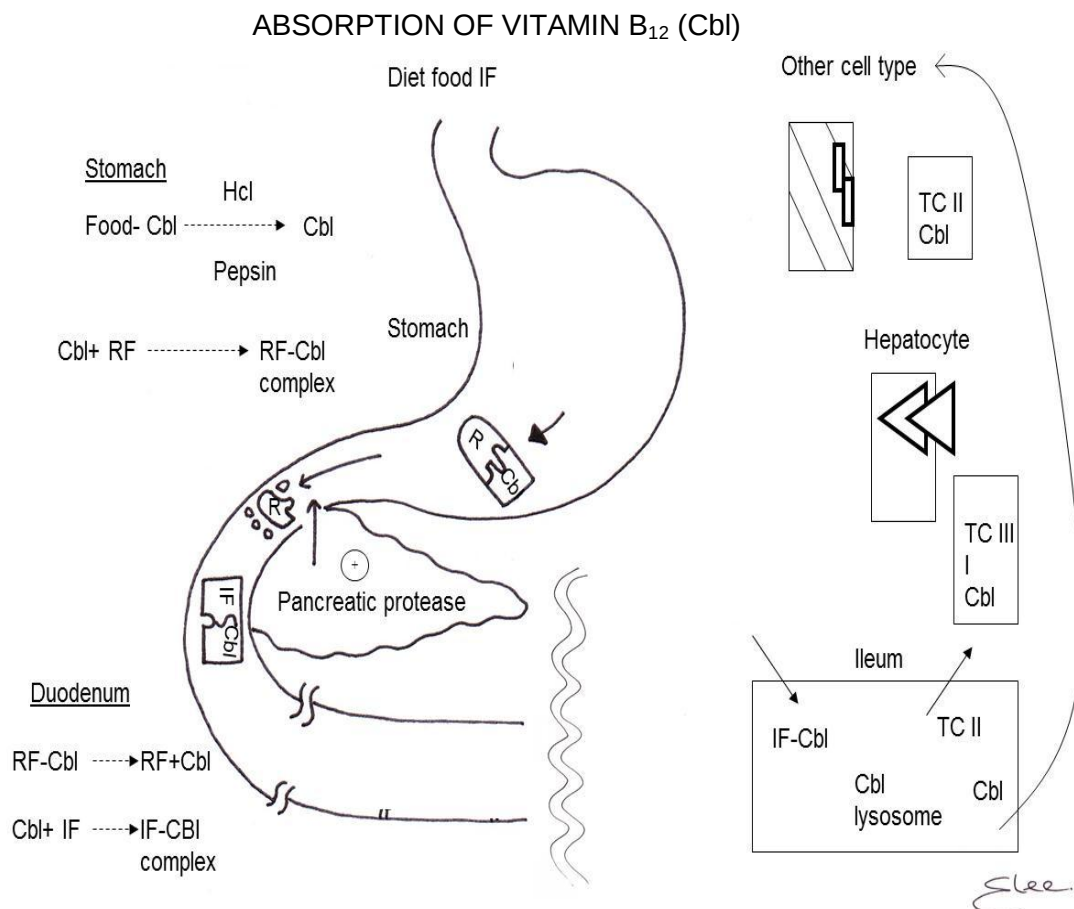
Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 45-15, page 970.

➤ Diet

- Dietary folate is comprised of pteridine, p-amino benzoates and seven glutamate molecules (PteGlu₇; aka folate polyglutamate or pteroylpolyglutamate).
- Dietary folate is similar to medicinal folate, other than having several glutamate residues.

- Jejunum – brush border (apical) membrane (AM)
 - AM folate conjugase (aka peptidase) removes (i.e., deconjugates) all but one glutamate from the dietary folate molecule, leaving PteGlu1 (monoglutamate).
 - PteGlu1 is transported into the enterocyte by the AM carrier Ste-Glu1.
 - Ste-Glu1 is a folate- OH^- exchanger
 - The pH optimum for AM folate conjugase and the folate- OH^- -exchanger Ste-Glu1 is 5.
- Cytosol
 - The PteGlu1 is metabolized in the enterocyte cytosol by difolate reductase to dihydrofolate (DHF).
 - DHF is further metabolized to the biologically active tetrahydrofolate (THF).
 - After the cell has reduced PteGlu 1 to THF by adding four H^+ s, it then converts THF to 5, 10 - methylene - THF, thus breaking down serine to glycine in the process.
 - This 5, 10 - methylene THF is the methyl donor in the conversion of the nucleotide deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) in the synthesis of DNA.
 - A second reaction converts this 5, 10- methylene-THF to N^5 - methyl-THF, which can then act as a methyl donor in the synthesis of methionine.
 - THF has three parts: the biologically active pteridine moiety, a p-aminobenzoate, and a glutamate.
 - THF traffics across the cytosol to the basal membrane (BM).
- Jejunum – BM
 - At the BM, an unknown carrier transports PteGlu1 and N^5 -THF into the portal circulation.

Vitamin B₁₂ (cobalamin, Cbl) Absorption



Abbreviation: Cbl, cobalamin (vitamin B₁₂); PP, pancreatic proteases; TC II, transcobalamine II; TC III, transcobalamine III

➤ Diet

- Cobalamin (Cbl) is synthesized by microorganisms, and dietary Cbl is ingested only in animal products.
- Some Cbl may also be present in bile.

➤ Stomach

- In the stomach, Cbl is released from animal proteins as a result of the actions of HCl and pepsin.

- The glycoprotein R factor (RF, aka, haptocorrin) is secreted by salivary glands and gastric glands.
- The free Cbl binds to haptocorrin.
- Haptocorrin preferentially binds Cbl at the acidic pH in the stomach
- Duodenum
 - Intrinsic factor is secreted by the gastric parietal cells.
 - If mixes with gastric juice, which is mixed with food, and is emptied into the duodenum.
 - Intrinsic factor secretion from the gastric parietal cell is stimulated by Ach, histamine and gastrin (just as is the case for the HCl secretion from the parietal cell).
 - Cbl is released from the RF-Cbl complex in the alkaline pH in the duodenum.
 - The Cbl now binds to IF in the presence of Ca^{2+} , rather than to R-factor.
 - Both the biliary and dietary Cbl bind to IF.
- Pancreas
 - Pancreatic proteases continue to digestion of protein to release Cbl
 - IF is resistant to pancreatic proteases, but the pancreatic proteases degrade the R factor.
- Ileum – enterocyte AM
 - The Cbl-IF complex passes along the small intestine to the ileum.
 - In the Ileum, a Cbl-IF carrier transporters the complex across the AM (brush border apical membrane).
 - In the cytoplasm of the ileal enterocyte, endosomes containing Cbl-IF are formed.

- The cytoplasmic lysosomes degrade the IF, and release Cbl back into the cytosol.
- The released Cbl in the ileal enterocyte cytosol is incorporated into secretory vesicles.
- The secretory vesicles are bound to trans-coalbumin II (TCII).
- The Cbl/TCII complex may be stored in the liver or secreted into bile.
- In the liver, Cbl acts as a coenzyme for H:MMT (homocysteine methionine methyltransferase). The methionine is a methyl donor for DNA synthesis.
- The secretory vesicle releases the Cbl-TCII complex across the basolateral membrane (BM) and into the portal circulation.

➤ Systemic Circulation

The steps in TC II – mediated cellular uptake and transport of cobalamin (Cbl) are as follows:

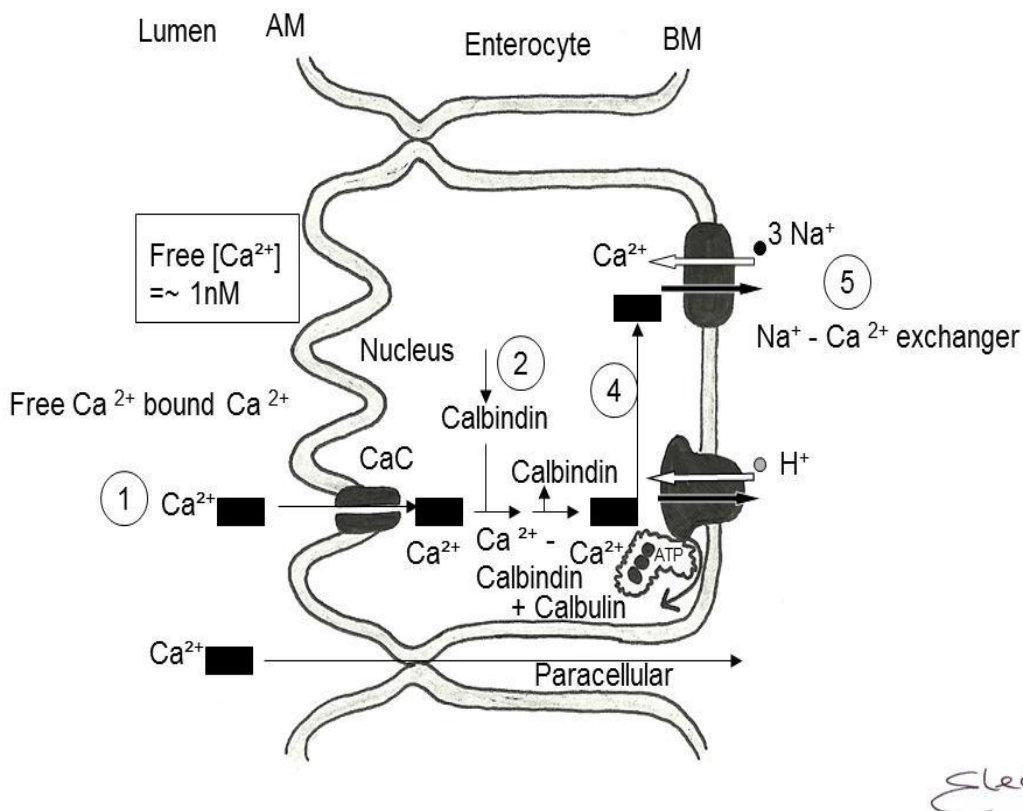
- 1) Binding to cell surface receptor
- 2) Internalize
- 3) Formation of secondary lysosome
- 4) Cbl release and TC II degradation
- 5) Coenzyme synthesis

Minerals

Calcium

- The bioavailability of Ca^{2+} depends upon the balance between free and bound Ca^{2+}
- Most Ca^{+2} is absorbed in the upper intestine.
- 1) Ca^{2+} crosses the AM through a Ca^{2+} channel (CaC).
- 2) In the cytosol, absorbed Ca^{2+} is bound to the protein “calbindin”.

- 3) The binding of Ca^{2+} calbindin reduces the intracellular concentration of Ca^{2+} .
- As a result of this lower concentration of intracellular Ca^{2+} , more Ca^{2+} crosses through the AM CaC.



Abbreviations: AM, apical brush border (apical) membrane; BM, basolateral membrane; CaC, calcium channel in AM; Ca^{2+} - H^{+} exchanger, calcium pump in BM

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009; Figure 45-17, page 974; and from *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-20, page 1723, Ninth Edition, 2010.

- The Ca^{2+} - calbindin complex traffics to the BM.
- 4) At the BM, Ca^{2+} is released from the Ca^{2+} -calbindin complex (Ca^{2+} - calbindin $\rightarrow$ Ca^{2+} + calbindin)
- 5) The Ca^{2+} crosses the BM by the energy (ATP) – dependent Ca^{2+} - H^+ exchanger (Ca^{2+} pump), as well as by the Na^+ - Ca^{2+} exchanger.
- Vitamin D (1,25-dihydroxyvitamin D) enhances Ca^{2+} absorption by three mechanisms:
 - increases Ca^{2+} uptake across the AM by the Ca^{2+} channel
 - increases the synthesis of calbindin
 - increases the transport of Ca^{2+} across the BM by the Ca^{2+} pump and the Na^+ - Ca^{2+} exchanger.

Magnesium (Mg^{2+})

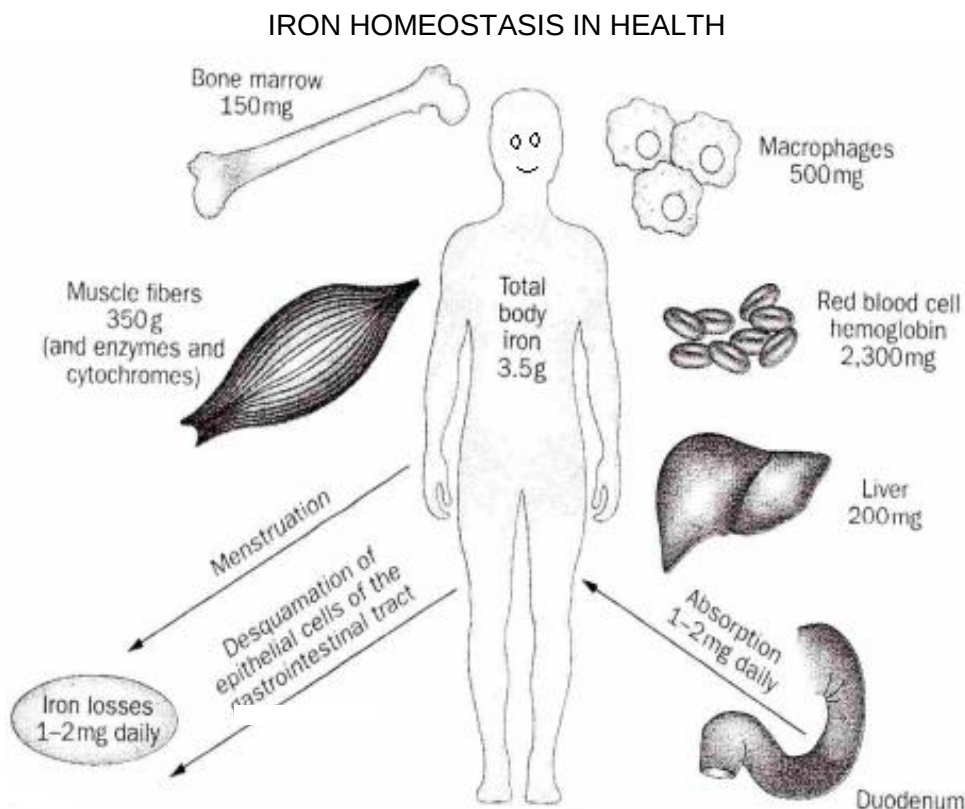
- Most Mg^{+2} uptake is carrier-mediated in the ileum.
- Lesser amounts of Mg^{+2} are absorbed along the length of the small intestine, presumably by passive diffusion.
- Mg^{+2} absorption is not influenced by vitamin D.

CLINICAL PHYSIOLOGICAL CHALLENGE – Water Absorption

Background: Water may be absorbed through the brush border membrane, or between the enterocytes. A person takes sips of water throughout the day, and with a meal.

Problem: Draw a picture of the absorption of water from along the intestinal tract where the person is eating, or just drinking water.

Iron balance



Adapted from: Stein J, et al. *Nat. Rev. Gastro. Hep.* Figure 1, page 599-610, 2010

➤ Storage

- Approximately 3500 mg of iron is stored by the human body.
- Most of the iron in the body is present in red blood cells as hemoglobin (~2,300 mg).
- Approximately 10% of body iron is present in myoglobin in muscle fibers, as well as in other tissues in enzymes and cytochromes (350 mg).
- The remaining body iron is stored in the liver (200 mg), macrophages (500 mg), as well as bone marrow (150 mg).

- About 1-2 mg of iron is lost daily from the body by way of the desquamation of epithelial cells of the skin, gastrointestinal tract, bile ducts and urinary tract, and via blood loss during menstruation.
- Blood and therefore iron may be lost from the body from bleeding caused by pathological processes, or through the generous donation of blood.
- The loss of iron from the body is not controlled
- Body iron balance is controlled by the modification of iron absorption by the intestine.

➤ **Luminal Factors and Iron Absorption (IA)**

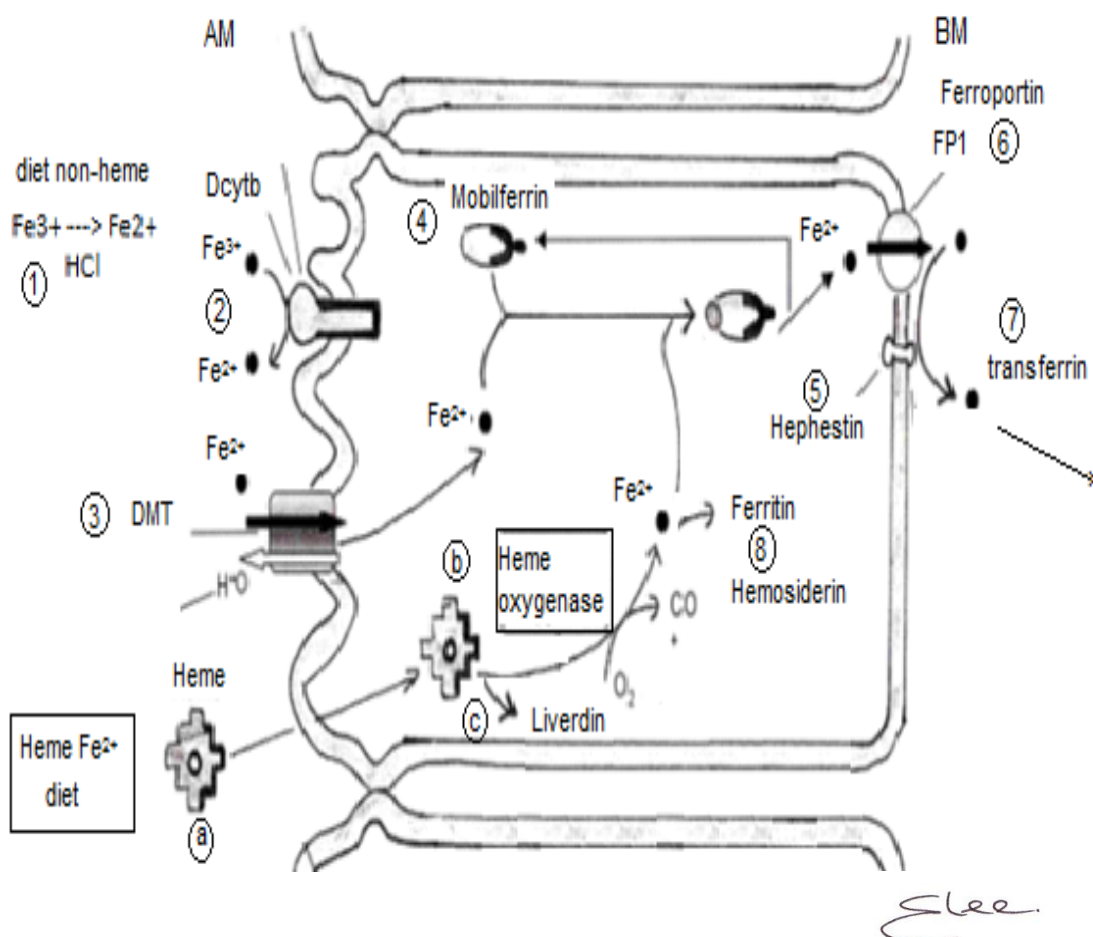
- Iron absorption from the digestive tract is the sole means by which iron homeostasis is regulated: (i.e., there is no regulation of iron secretion or loss from the body).
- Duodenal enterocytes are the major site of Fe^{2+} absorption.
- There are numerous luminal factors which increase or decrease iron absorption (IA).

Increase (IA)	Decrease (IA)
○ Reducing agents – HCl – Ascorbic acids ○ Chelating agents – Organic acids – Amino acids	○ Intraluminal binders – Phosphate – Phylates – Oxalates – Dietary fiber

➤ **Enterocyte AM digestion and absorption**

- 1) Non-heme Fe^{3+} is reduced to Fe^{2+} by HCl with gastric lumen.
- 2) Non-heme Fe^{3+} is also reduced to Fe^{2+} by the duodenal enterocyte AM, ferric reductase [Dcytb].

- Fe^{2+} , arising from dietary Fe^{3+} in the gastric lumen, is solubilized by chelating agents such as ascorbic acid, amino acids and organic acids.
- 3) Fe^{2+} from non heme Fe^{3+} crosses the duodenal AM by the Fe^{2+} - H^+ transporter DMT1 (divalent metal transporter aka SLC11A2, which cotransports Fe^{2+} with H^+).



Abbreviations: AM, apical (brush border) membrane; BM, basolateral membrane; Dcytb, duodenal cytochrome B; DMT1, divalent cation transport 1; HCP1, heme carrier protein 1; Hox1, heme oxygenase

Adapted from: *Medical Physiology*, Second Edition, Boron Walter F. and Boulpaepemile L. 2009, Figure 45-18, page 975; and from *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 100-21, page 1724, Ninth Edition, 2010

➤ Enterocyte cytoplasm

- In the cytosol (as well as in other parts of the body, Fe^{3+} may be bound to the storage protein ferritin
- 4) In the cytosol, Fe^{2+} binds to mobilferrin.
 - At the BM, Fe^{2+} is removed from mobilferrin by FP1.
- Fe – mobilferrin diffuses to the BM.
- 5) At the BM, Fe is oxidized to Fe^{3+} by hephaestin.
- 6) The Fe^{3+} binds to BM FPI (ferroportin transporter, aka IREE1) as is transported into the portal blood.
- 7) Fe^{3+} in portal blood is bound to transferrin
- Mobilferrin traffics back to the AM to bind to more non-heme Fe^{2+} ..

➤ Plasma Iron

- 8) Some Fe^{3+} which is bound to plasma transferrin moves back across the BM into enterocytes, where the Fe^{3+} is bound to apoferritin.
- Apoferrin plus Fe^{3+} form soluble protein “ferritin”.
- Ferritin is the major storage form of iron, and ferritin may be detected in the blood as well as in tissues.
- Some iron in the cell is bound to hemosiderin. Hemosiderin is insoluble and remains in the cytoplasm.

• Heme-Iron

- a) Heme- Fe^{2+} crosses the AM by an unknown mechanism.
- b) In the cytosol of the enterocyte, heme oxygenase (Hox1) oxidizes the heme- Fe^{2+} to Fe^{3+} .
- In the cytoplasm of the duodenal enterocyte, Fe^{3+} either binds to ferritin or is transported across the BM by means of ferroportin.

- c) The remaining biliverdin in heme is reduced to bilirubin, which is eventually excreted in bile (please see the Liver Chapter, excretion of bilirubin)
- Control of Body Iron Stores (BIS) by the Modification of Iron Absorption in the Intestine
 - Please see the Liver Chapter for more information on the role of the liver in the control of iron absorption, and the roles of the liver and proximal small intestine in the development of hereditary iron overload (hemochromatosis)
- Body Iron Stores
 - Hepcidin (HFE protein), hemojuvelin (HJV) and transferrin receptor 2 (TFR2) participate in the hepatic iron-sensing mechanism that regulates hepcidin expression.
 - HFE is secreted in hepatic Kupffer cells in an amount which is inversely related to body iron stores (BIS). ($\uparrow$ BIS - $\downarrow$ HFE; $\downarrow$ BIS - $\uparrow$ HFE)
 - Iron absorption in enterocytes activates BMP6 expression, and the delivery of BMP6 to the liver.
 - In the liver, BMP6 binds to type I and II receptors (BMPRI and BMPRII) as well as to the co-receptor HJV.
 - BMP6 bound to BMPRI and HJV phosphorylates SMAD1, SMAD5 and SMAD8, and complex formation with SMAD4.
 - When the body iron stores (BIS) are low, BMP (bone morphogenetic protein) senses the enteric iron status.
 - Hepatic Kupffer cells secrete less hepcidin into the blood.
 - Hepcidin reduces iron release by macrophages (and thereby increases macrophage iron stores) and also reduces iron absorption by duodenal enterocytes, by moving FP1 away from BM, to reduce the amount of dietary iron in the circulation.
 - Less hepcidin upregulates DMT1 and FP1, thereby increasing Fe^{+2} AM uptake into and Fe^{3+} BM transfer out of the duodenocyte.

- Increased uptake and transfer of iron continues until the low BIS have been restored to normal.
- Once the BIS are normal, hepcidin falls, and the DMT1 – FP1-mediated increased iron absorption returns to the normal lower level of iron uptake across AM and exit across BM.
- IL-6
 - Iron absorption is inversely related to body iron stores (BIS), and to the level of the pro-inflammatory cytokine IL (interleukin)-6.
 - Higher levels of IL-6 stimulate the hepatic secretion of hepcidin.
 - Hepcidin gene expression is up-regulated during infection and inflammation by proinflammatory cytokines – mainly IL-6 (involving JAK dependent activation of STAT3).
 - With ↑IL-6 and ↓ hepcidin, less iron is released from duodenocytes and from macrophages
- HFE – related hereditary hemochromatosis (HH)
 - In HH, loss of functional HFE protein leads to aberrant hepatocellular sensing of plasma iron, inappropriately low levels of hepcidin, diminished macrophage iron stores, and greater duodenal iron absorption.

CLINICAL PHYSIOLOGICAL CORRELATION – Iron Metabolism

Background: In *HFE*-related hereditary hemochromatosis, loss of functional HFE protein leads to aberrant hepatocellular sensing of plasma iron, with inappropriately low levels of hepcidin, diminished macrophage iron stores, and inappropriately greater duodenal iron absorption.

Problem: Draw a picture of the absorption of dietary iron by the duodenal enterocyte, and the role of both the intestine and the liver in causing hereditary hemochromatosis.

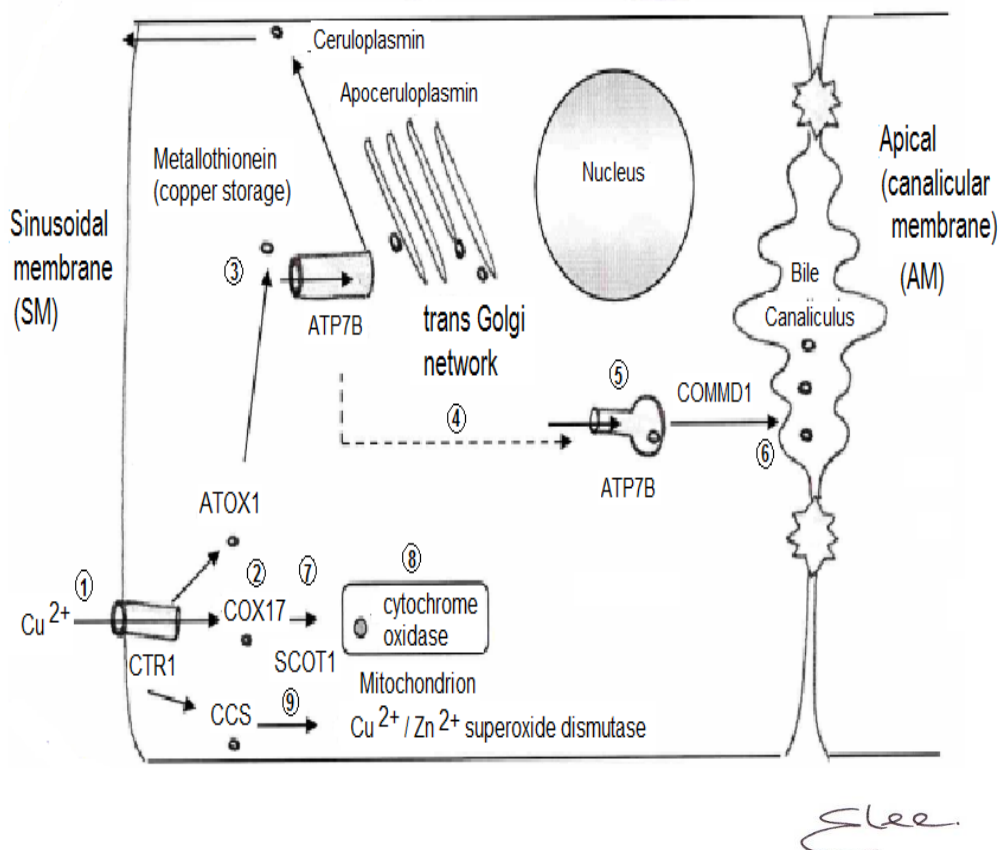
Copper

➤ LIVER COPPER METABOLISM AND TRANSPORT PATHWAYS

- 1) Cu^{2+} across SM in CTR1 and is bound to ATOX1, COX17 or CCS.
- 2) In the hepatocytes, the low-molecular-weight copper chaperones ATOX1, COX17, and CCS deliver copper to the specific target proteins ATP7B, cytochrome oxidase and superoxide dismutase, respectively).
- 3) Cu^{2+} bound to ATOX1 binds to ATP7B.
- 4) ATP7B traffics to the trans-Golgi network (TGN) in the hepatocyte cytoplasm.
- 5) ATP7B binds to COMMD.
- 6) Cu^{2+} bound to COMMD is excreted across the AM.
- 7) Cu^{2+} bound to COX17 binds to SCO1.
- 8) SCO1 transports Cu^{2+} across the mitochondrial membrane.
- 9) Cu^{2+} bound to CCS is acted on by $\text{Cu}^{2+}/\text{Zn}^{2+}$ superoxide dismutase.

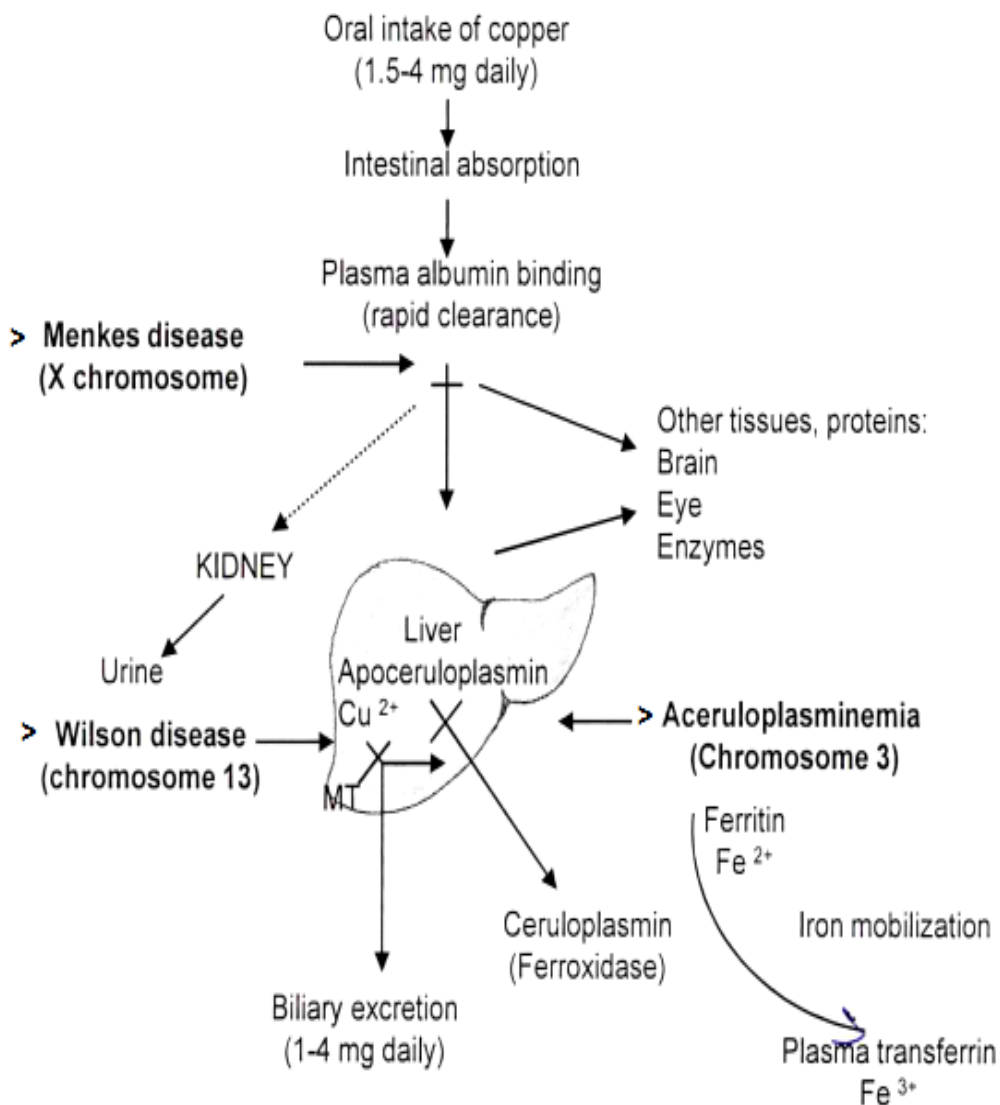
➤ SMALL INTESTINE

- In the enterocytes Cu^{2+} is absorbed by active and p



Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figures 75-1 and 75-2, page 1250, Ninth Edition, 2010; and Cox DN. *Am J Hum Genet* 1995;56:828-834.

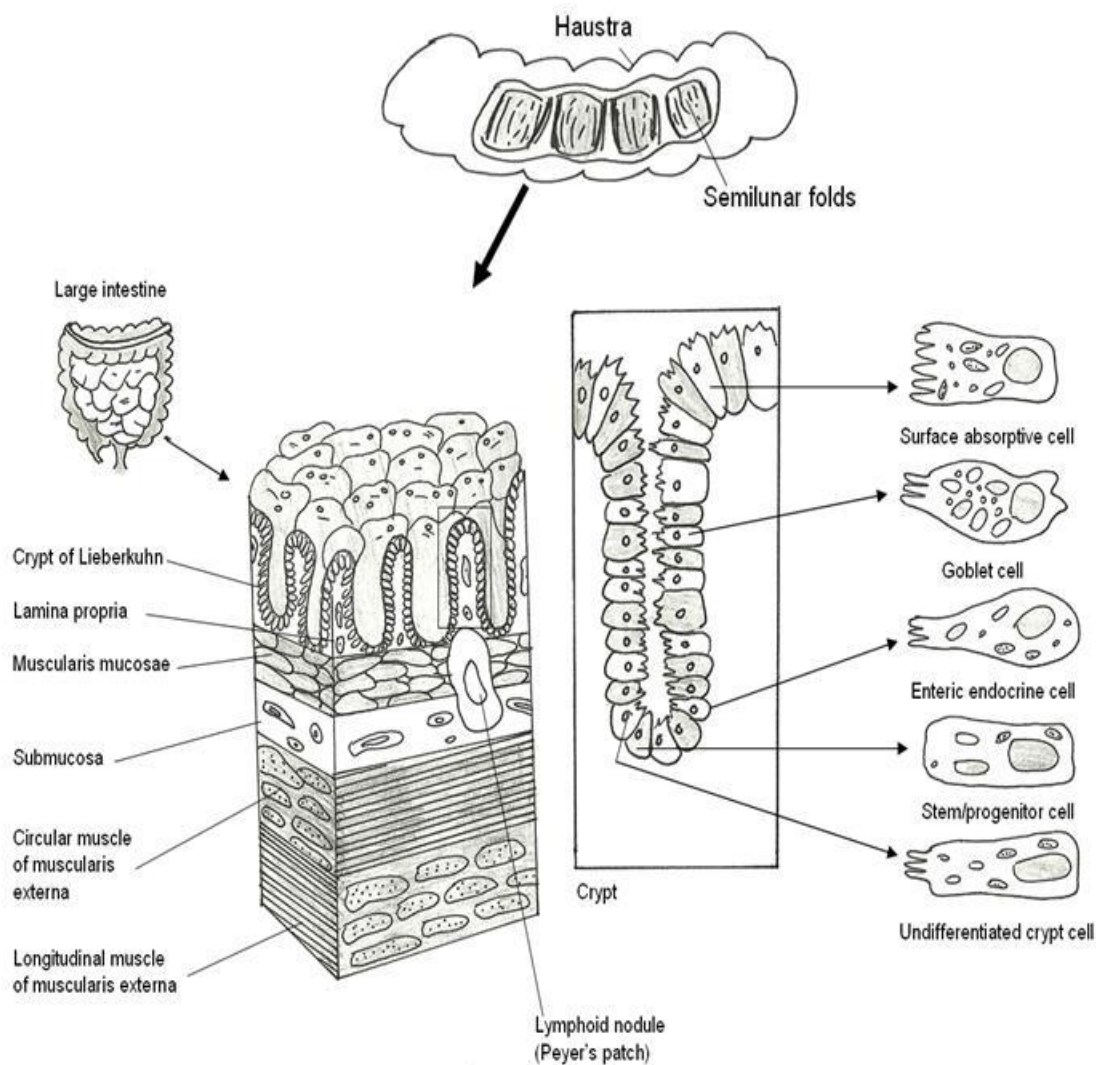
DISORDER OF THE COPPER METABOLISM



Elee.

COLON

Structure



See

Adapted from: Medical Physiology, Second Edition, Boron Walter F. and Boulpaepemile L. 2009, Figure 41-3, page 885.

**Scientific Basis for Clinical Practice in
Gastroenterology and Hepatology**

- The wall of the colon is comprised of an inner circular and an outer longitudinal muscle layer.
- The longitudinal muscle layer is discontinuous, running in three 6-to-10 mm wide bands (teniae coli) from the cecum to the rectum.
- There is no muscle between the teniae coli, leading to three bulges in the wall of the colon, called the “haustra”.
- The haustra are between the teniae coli
- Because these muscles are tonically contracted and then suddenly relax, their size changes with contraction and relaxation of the muscle bands.
- When the muscle coats contract, the flat mucosal surface of the colon appears as folds, known as the semilunar folds or the plicae semilunaris.
- The cecum, ascending and descending colon are less mobile than the transverse colon and sigmoid colon, each of which has a mesentery.
- The ileocecal valve (ICV) appears as two transverse folds.
- The ICV is anatomically not a sphincter, but has a resting tone of 20 mm Hg and so is capable of functioning in this manner.
- When the terminal ileum is distended, the ICV pressure falls so that small intestinal contents pass into the cecum.
- The (vermiform) appendix is attached to the medial wall of the cecum of adults. Its function in humans is unknown.
- The S-shaped sigmoid colon is angulated, particularly at the rectosigmoid junction, where the colon begins to have a peritoneal surface.
- The colonic mucosa becomes smoother in the rectum, which passes between the sacrum and the uterus in females, or between the sacrum and the bladder in males.
- The inner circular muscle of the colon becomes thicker and ends as the internal anal sphincter (IAS).

- A layer of elastic fibers and the outer longitudinal layer of the rectum separate the IAS from the outer external anal sphincter (EAS).
- The EAS is skeletal muscle, and is under voluntary control.

Main diseases

- Increase or decrease in stool output (diarrhea/constipation)
- Fecal incontinence
- Inflammatory bowel disease (IBD; Crohn disease or ulcerative colitis)
- Irritable bowel syndrome (IBS)
- Colorectal cancer (CRC)

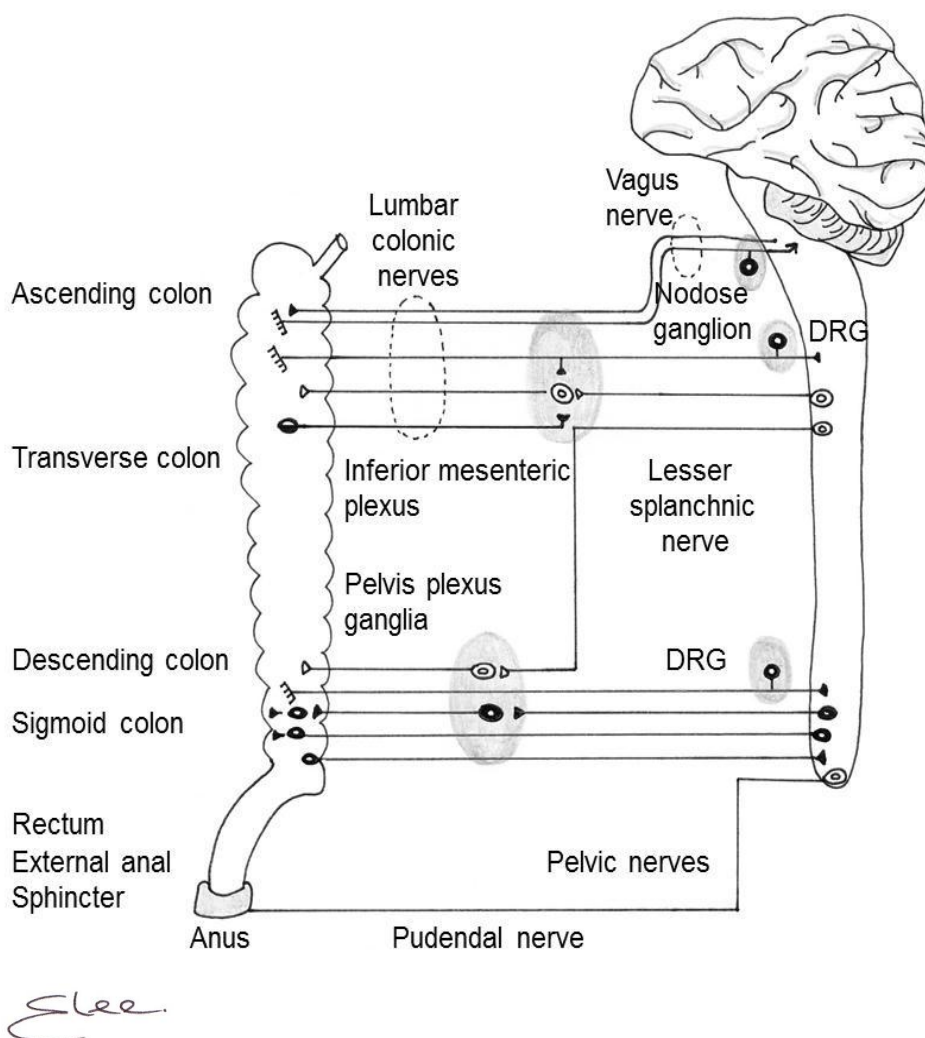
Movement/Transit

- The functions of the colon include mixing, absorption/secretion of water, metabolism, transit, storage, and control of fecal evacuation.
- Colonic transit is controlled by the parasympathetic and sympathetic nervous systems

Parasympathetic and Sympathetic Nervous System

- Enteric nerve cell bodies in the colon receive input from both parasympathetic and sympathetic pathways.
- Extrinsic nerves provide a greater control over the colon than over the small intestine.
- Parasympathetic efferent pathways from the dorsal motor nucleus of the vagus in the brainstem pass through the vagus nerve to the colon and through prevertebral sympathetic ganglia to the colon, through the lumbar colonic nerves.
- Parasympathetic pathways from nuclei in the sacral spinal cord also run through the pelvic nerves and either synapse in the pelvic plexus ganglia, or run directly into the colonic wall.

INNERVATION OF THE COLON



Abbreviations: DRG, dorsal root ganglia

Adapted from: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Figure 98-3, page 1662, Ninth Edition, 2010

- Sympathetic pathways consist of preganglionic neurons which project out of the prevertebral ganglia.
- Viscerofugal enteric neurons project out of the bowel to the prevertebral ganglia.

- There are also spinal afferents with cell bodies in dorsal root ganglia (DRG) which run
 - through both the lesser splanchnic and lumbar colonic nerve pathway, and
 - via the pelvic nerves and ganglia to the rectum.
- These include sensory neurons that transmit non-nociceptive information about the distention of the rectum.
- Afferent pathways consist of vagal neurons from the proximal colon with cell bodies in the nodose ganglion (NG).
- These synapse with sympathetic postganglionic neurons, either in the inferior mesenteric plexus or in the pelvic plexus.

➤ CCK and Motor Activity

- The tonic ring contractions are myotonically produced.
- The pacing of the regular rhythmic contractions is by way of electrical slow waves, slower in the colon (every 10 sec.) versus faster in the small intestine (every 6 sec).
- After eating and the entry of food into the duodenum, there is release of CCK.
- CCK increases the neurally mediated motor function of the ileum and the colon (especially the sigmoid colon), known as the “gastrocolic reflex”.
- The movement (transit, aka craniocaudic translocation) of feces is more marked in the colon than is the mixing flow.
- Flow from the stomach to the cecum takes 1-2 hours, but flow from the cecum to the rectum takes 5-7 days.
- Transit through the transverse and descending colon is relatively faster than through the rest of the colon.
- The pudendal nerve (S2) supplies the pelvic diaphragm (PD) and external anal sphincter (EAS); S3 and 4 nerves supply the puborectalis.

- Extrinsic sympathetic and parasympathetic /afferent and efferent nerves from the lumbosacral cord run through the pelvic plexus and innervate the internal anal sphincter (IAS) and the rectum.
- Motor activity in the proximal colon (cecum, ascending and transverse colon) are controlled by myogenic, neurogenic (vagus and pelvic nerves) and hormonal factors.
- This motor activity causes
 - mixing (non-propulsive segmentation caused by slow wave activity, creating haustra), and
 - peristalsis (mass peristalsis, propulsion distally of fecal material)
- Motor activity in the distal colon is mostly segmentation, until a mass peristalsis fills the rectum and the process of defecation is begun.
- A lump of feces will move quickly over several centimetres, then stop for awhile, then propel forward again; these are called “mass movements”.
- The mass movements occlude the colonic lumen, push in the caudal direction and gradually fill the rectosigmoid bowel.
- The intermittent rhythmic contractions that cause the mass movement of feces are neurogenic, initiated by extrinsic innervation, and are not linked to electrical slow waves.
- During the intermittent ring contractions, the haustra temporarily disappear.

CLINICAL PHYSIOLOGICAL CHALLENGE – Constipation

Case: A 30 year-old mother of three pre-schoolers presents with a 3 month history of increasing constipation, by which she means three BM's per week, passing hard stools. There is no abdominal pain and no rectal bleeding. She is otherwise well.

Questions: Give the normal physiology of colonic transit. Classify the medications used to treat constipation. Give the safety of these medications during pregnancy and lactation.

Classification of Laxatives

Laxative class	Laxative agents	Mechanism of active	Potential limitations
➤ Bulk laxatives	○ Natural fibre (e.g. psyllium seed husk) ○ Semisynthetic fibre (e.g. methylcellulose) ○ Synthetic fibre (e.g. polycarbophil, polyethylene glycol macogol)	– Luminal water binding increases stool bulk and reduces consistency	– Abdominal distention
➤ Osmotic salts	○ Magnesium hydroxide, Magnesium citrate, Magnesium sulphate, Sodium phosphate	– Osmotic water binding	– May cause electrolyte abnormalities; to be used with caution in patients with renal or cardiac failure
➤ Disaccharides and sugar alcohols	○ Lactulose ○ Sorbitol	– Osmotic water binding	– Bacterial fermentation with bloating, flatulence, less effective in slow transit due to bacterial degradation
➤ Stool softener	○ Paraffin oil ○ Docusate	– Luminal water binding increases stool bulk and reduces consistency	– Abdominal discomfort and cramps

Laxative class	Laxative agents	Mechanism of active	Potential limitations
➤ Stimulant laxatives	○ Diphenylmethane derivatives (bisacodyl, sodium picosulphate) ○ Anthraquinone derivatives (senna, aloe, cascara)	– Induce colonic contractions by acting on enteric nerves – Decrease colonic absorption of water and electrolytes	– Abdominal discomfort and cramps

Printed with permission: Tack J. Current and Future Therapies for Chronic constipation. *Best Practice and Research Clinical Gastroenterology* 2011; 25: 151-158.

Intestinal Gas

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q1. Name 6 major intestinal gases.

- A1.
 - From inspired air – N₂, O₂, CO₂
 - from metabolism – H₂, CH₄, CO₂, H₂S

Q2. Why is it suggested to persons with “intestinal gas” to eat slowly and to drink at the end of meals?

A2. For every 10 mL of fluid consumed, we swallow about 18 mL of air! (aerophagia)

Q3. What is the mechanism to explain why breath Hydrogen levels may be falsely low and thereby misrepresent the presence of SIBO (small intestinal bacterial overgrowth)?

A3. H₂ is produced by intestinal bacteria, some of which consume H₂ to reduce sulfate to sulfide, or use H₂ to reduce O₂ to CH₄ (methanogenic bacteria).

Q4. After eating garlic – containing foods, why does flatus not smell of garlic?

A4. The odoriferous (“smelly”) sulfur-containing gas which is derived from garlic is absorbed and excreted in the breath, not in the stools.

SO YOU WANT TO BE A GASTROENTEROLOGIST!

Q5. What is the normal 24-hour volume of passage of flatus, and the number of individual passages?

A5. The average person passes per rectum about 2200 mL of flatus per day, falling to about 400 mL per day and a low-fiber diet. The frequency of passages ("farts") is about 10 per day.

Q6. What is the relative rate of passage of substances along the GI tract?

A6. Gas faster than liquids or solids.

Q7. Distinguish between the terms "bloating" and "distention"?

A7:

- Bloating – "subjective sensation of a swollen abdomen, full belly, abdominal pressure, or excess gas" (no correlation between measured/ intestinal content of gas and symptom of bloating – symptom of bloating is due to a disturbance in the gas.
- Distention ".... an objective increase in [abdominal] girth". (S/F page 238)

Defecation

- Maintenance of fecal continence, and the process of defecation, is a complex and integrated process.
- Continence of stool is controlled by the internal and external anal sphincters, the rectum, the pelvic diaphragm, and the coordinated innervation of these of these structures.
- The striated muscles of the pelvic floor (including the external anal sphincter) are supplied by motor neurons with cell bodies in the spinal cord and with axons that run in the pudendal nerves (S2).
- Rectal compliance increases, the intraluminal does not increase, and the rectum continues to receive stool.
- As feces enters the rectum, the rectum expands and the sensory mechano- and chemoreceptors are stimulated, giving the sensation of "the urge to purge".

Muscles involved in defecation

Condition	Type of Muscle	
	Skeletal Muscle	Smooth Muscle
➤ At rest	➤ Relax ○ Puborectalis ○ EAS	➤ Relax ○ IAS
➤ Contract ○ Puborectalis ○ EAS, IAS	➤ Contract ○ Diaphragm (moves down) ○ Levator ani (moves up) ○ Rectus muscle (moves inwards)	➤ Contract ○ Rectum ○ Urge to purge

Abbreviations: EAS, external anal sphincter; IAS, internal anal sphincter

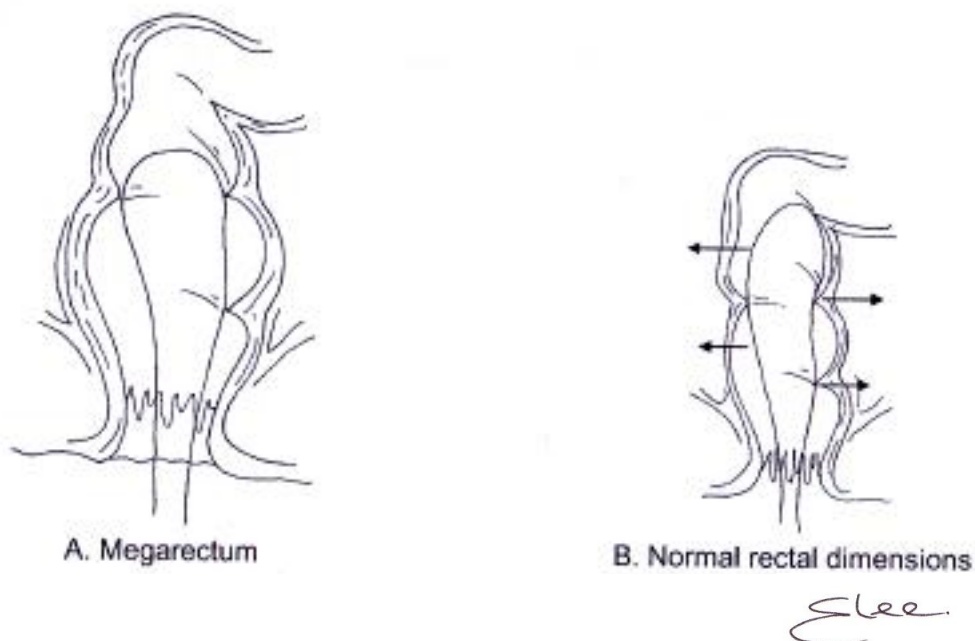
CLINICAL PHYSIOLOGICAL CHALLENGE – Fecal incontinence

Case: A 60 year old mother of three children presents with fecal incontinence. There is no overflow diarrhea or urinary incontinence.

Questions: Give

- The physiology of defecation
- The approximate normal values of anorectal sphincter pressure and volumes of balloon distention to achieve rectal sensation.
- The tests used to investigate fecal incontinence, including sensory, motor and biomechanical function, as well as rectal capacity and composite sensory motor function.
- The medical, endoscopic and surgical treatments of fecal incontinence.

IMPACT OF RECTAL SIZE ON SENSORY THRESHOLD VOLUMES



- With a megarectum (A) greater volumes will be required to initiate distension, and thus to elicit rectal sensations during balloon distension, as compared to those with normal rectal dimensions (B).

Adapted from: S. M. Scott et al., *Best Practice and Research and Clinical Gastroenterology* 2011; 25: 103-118.

- The spongy vascular tissue underneath the squamous epithelium in the anal canal are also important to maintain fecal continence.
- Normally the puborectalis muscles (PR) is contracted, so that there is a sharp 90° angle between the axis of the rectum and the anal canal. When the PR muscle relaxes, the rectoanal angle becomes <90°.
- The levator ani is comprised of three muscles (puborectalis, pubococcygeus, and ileococcygeus) which form the pelvic diaphragm and a puborectal sling.
- When the levator ani contracts, there is a rise of the pelvic diaphragm (PD), the rectum and anus.

- This rise in the PD causes a decrease of the anal-rectal angle, and straightening of the rectum.
 - When the pelvic floor relaxes, the anal-rectal angle increases.
 - Receptors lead to reflex relaxation of internal anal sphincter (IAS).
 - The myotonically-produced tonic ring contraction involves the IAS.
 - The tone in the IAS is reduced or increased by neurogenic mechanisms (NANC inhibitory and cholinergic stimulatory motor nerves).
 - The striated and voluntarily-innervated skeletal muscle of the external anal sphincter (EAS) surrounds the IAS.
 - Signals also arise in the rectus muscles of the abdominal wall and thorax, stimulating central sensory pathways.
 - The defecation reflex is initiated from these local and central afferents; a ring contraction beginning at the rectosigmoid junction, relaxation of the levator ani muscles, leading to relaxation of the IAS through NANC nerves.
 - The pelvic diaphragm is composed of the levator ani, puborectalis, pubococcygeus and ileococcygeus skeletal muscles. The pelvic diaphragm has holes through which pass the urethra, rectum, and vagina in females.
 - When the IAS relaxes and intraabdominal pressure is voluntarily increased, defecation occurs.
 - The function of the IAS may be assessed clinically by rectal manometry, a test which may be performed as part of the investigation of the incontinence:
 - Once defecation occurs, the rectosigmoid colon becomes empty, and is ready to be filled again with the mass movement of feces.
- Nerve supply
- Anorectum
 - Sensory and motor function of pudendal nerve (S2 to S4)
 - Rectum (distention)

- S2 to S4 parasympathetic nerves, which travel with the splanchnic (and not the pudendal) nerves
- Parasympathetic stimulation contracts and sympathetic stimulation relaxes.
- Rectal mucosa and myenteric plexus – myelinated and unmyelinated nerve fibers which mediate:
 - Reflexes (viscerovisceral, rectoanal contractile and sympathetic reflex)
 - Stretch (distentions) causes
 - rectoanal inhibitory reflex, with ↓ resting pressure
 - rectoanal contractive reflex response
- Puborectalis muscle – may contain sensory receptors to distinguish between flatus and feces (sampling reflex)

Fecal Continence

➤ The anatomical components of fecal continence

- Anus – 2 cm to 4 cm muscular tube, closed at rest
- Anorectal angle
 - At rest, 90°
 - Squeeze, 70° (acute)
 - Defecation, 110 – 130° (obtuse)
- Internal anal sphincter (IAS) – 0.3 cm to 0.5 cm expansion of rectal smooth muscle.
- External anal sphincter (EAS) – 0.6 cm to 1.0 cm expansion of levator ani muscles.
- Contributions of pressure of anal sphincter (IAS plus EAS), %

		IAS	EAS
-	Resting	75	25
-	Response to distention		
	▪ Sudden	40	60
	▪ Constant	65	35

- Seal of anus
 - Tonic activity of IAS plus EAS

- Anal mucosal folds
- Anal vascular cushions
- Flap – like valve of puborectalis muscle

Useful background: Q&As

- Give the approximate % contribution of various mechanisms of the development of fecal incontinence

Mechanism	%
○ Dysfunction of anal sphincter	75
○ ↓ pudendal nerve function	50
○ ↓ rectal sensation	50
○ ↓ rectal compliance	40

For complete details of mechanisms, causes, and pathophysiology of fecal incontinence, see *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, Table 171, page 243, Ninth Edition, 2010.

Fecal Incontinence

- When any of the normal components which contribute to fecal continence are dysfunctional, fecal incontinence (FI) may develop
- Fecal incontinence (FI) is a frequent cause of major embarrassment to sufferers
- FI is common in the elderly, infirm, after obstetrical injury
- FI may occur with diarrhea, and the patient with diarrhea must be carefully questioned, since they may really be suffering from incontinence

SO YOU WANT TO BE A GASROENTEROLOGIST!

Q1. In the context of fecal incontinence, what is “rectal agnosia”?

A1. Rectal agnosia is loss of the normal sampling reflex, leading to loss of the ability to distinguish between flatus and feces.

Q2. What is the “anal wink”, and what is the significance of its loss?

A2. Loss of the normal contraction of the EAS on touching the perianal skin to elicit the anocutaneous reflex (“anal wink”) suggests impaired afferent or efferent nerve damage.

SO YOU WANT TO BE A GASROENTEROLOGIST!

Q3. What is the use of neurophysiologic testing to measure PNTML (pudendal nerve terminal motor latency time)?

A3. PNTML accesses the function of the pudendal nerve, a cause of fecal incontinence. Unfortunately, pudendal neuropathy may be present even in the presence of a normal PNTML time (false-negative). Also note that symptom assessment does not always correlate with the severity of manometric findings.

Q4. What is “biofeedback therapy”, and in what type of incontinence is biofeedback training most effective?

A4. Biofeedback therapy is a form of neuromuscular training which is based on techniques of operant conditioning. The intention of feedback training is to improve.

- The strength of the muscles of the anal sphincter
- Anorectal sensation
- Coordination of the muscles involved with voluntary contraction after rectal distention (abdominal, gluteal, EAS).
- Biofeedback is as effective as electrical stimulation of the pudendal or sacral nerve.

Techniques used to Investigate Fecal Incontinence

Function	Test	Parameters measured
➤ Sensory function	○ Latex ballon distension ○ Barostat bag distension ○ Electrical stimulation ○ Brain 'image'	– Threshold volumes – Threshold volumes and pressures – Mucosal electrosensitivity thresholds – Mucosal thermosensitivity thresholds – Rectal evoked potentials – Function magnetic resonance imaging
➤ Motor function	○ Prolonged manometry ○ Prolonged barostat	– Phasic contractile activity – Tonic contractile activity, phasic contractile events
➤ Biomechanical function	○ Barostat pressure-volume curve ○ Impedance planimetry	– Compliance – Compliance, rectal wall stress and strain
➤ Capacity / size	○ Barostat study under fluoroscopy ○ MRI	– Diameter – Rectal dimensions
➤ 'Composite' sensorimotor function	○ Ballon expulsion ○ Evacuation proctography ○ MR defaecography	– Evacuatory function – Evacuatory function – Evacuation function

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Rectal Manometry

- Anorectal Sphincter Pressure*
 - Anorectal sphincter resting pressure 58 mm Hg
 - Pressure squeeze during voluntary contraction 130 mm Hg
 - Rectal pressure during straining 34 mm Hg
 - Duration of the voluntary contraction 12 sec
- Rectal Sensation
 - Balloon volume at first rectal sensation 100 cc ml
 - Balloon volume at defecation urge 180 cc ml
- Balloon Expulsion Test 12 sec
- Inhibitory Anorectal Reflex Present
- Rectal Compliance 1.6-5 cc/mm Hg

*Approximate Normal Values used in Clinical Practice

- When the colon pushes stool into the rectum, the rectum adapts, stretches and stores the stool
- When the rectal distention reaches a point where the person senses the distention, vagal effects are stimulated
- If the person wished to wait to have a “bowel movement” (BM), s/he voluntarily causes the stimulation of the external anal sphincter (EAS), and the stool stays in the rectum
- If the person wishes to respond to the sensation of rectal distention and to have a BM, they push down with their abdominal muscles, tighten the pelvic floor, and relax the EUS
- The vagal efforts cause the internal anal sphincter (IAS) to relax, the puborectalis relaxes, the rectum straightens, and stool is expelled

MISCELLANEOUS TOPICS

Mucosal Immunity

Useful background: Q&As

- Give the components of GALT (gut-associated lymphoid tissue)
 - PP (Peyer's patches) in the lamina propria
 - DCs (dendritic cells)
 - DCs directly sample self- and non-self-antigens in the intestinal lumen, and together with macrophages, DCs internalize these antigens and contribute to the induction of immune tolerance
 - FAE (follicle – associated epithelium)
 - M cells (microfold cells; a conduit to PPs by way of macrophages and DCs)
 - Macrophages
 - Antigen-presenting cells (APC; such as DCs, B lymphocytes, macrophages presenting antigen to T lymphocytes)
 - APCs (macrophages, monocytes, dendritic cells)
 - Process extracellular proteins from class II MHC molecules to CD4+ T cells
 - Process intracellular proteins from class I MHC molecules to CD8+ T cells
 - Non – MHC class I molecules interact with CD 8+ T cells
 - Lamina propria dendritic cells, Peyer's patches express IL-4, IL-10
 - T and B lymphocytes (activated in PPs to express integrin $\alpha 4\beta 7$
 - The lamina propria (LP) is the main effector site of GALT
 - MLNs (mesenteric lymph nodes; $\alpha 4\beta 7$ – containing lymphocytes home to Mad CAM-1 ligands)
 - IELs (intestinal epithelial lymphocytes, contributing to innate and to adaptive immunity)

- IECs
 - Transepithelial antigen transport
 - Most food proteins are hydrolyzed to non-immunogenic peptides and amino acids
 - 2% of food antigens (mostly glycoproteins) are absorbed
 - Transport ↓ - food, acid
 ↓ - alcohol, alkalinity
 - Phase I
 - Antigen – specific IgE antibodies bind to Fc R on surface of IECs
 - Fc R accelerates transfer of antigen
 - Mast cell – independent
 - IgE antibody band to IEC
 - Phase II
 - Mast cell – dependent
 - Mast cells release cytokines
 - IELs express cytokine receptors (IL-1, -2, -6, -10, -12, -15, GM-CSF [granulocyte – monocyte colony – stimulating factor], and IFN- γ [interferon - γ])
 - TJs open
- PAMPs (pathogen – associated molecular patterns; receptors for PAMPs on cell surface [e.g., TLRs] or in cells [e.g., NOD2])
- MHC (major histocompatibility complex [in rodents], known as HLA in humans)
- Costimulatory molecules for activation of CD⁸⁺ regulatory T cells (examples: ICAM-1, LFA-1, B7[CD80])
- LPLs (lamina propria lymphocytes), including LPMNCs (lamina propria mononuclear cells), e. g., IgA⁺-plasma cells)
- Microbiota – play circle in the induction of oral tolerance

- In healthy persons, the intraepithelial cells (IECs) stimulate regulatory CD8⁺ T cells.
- In IBD, the IECs stimulate CD4⁺ T cells.
 - Intraepithelial lymphocytes (IELs) – Th1 and Th2
- >98% of IELs are T cells, mostly $\gamma\delta$ TCR (rather than $\alpha\beta$ TCR in the systemic immune system)
- STAT – 4 $\rightarrow$ $\uparrow$ IFN - $\delta \rightarrow$ activates STAT-1 and T-bet
- T-bet
 - $\uparrow$ Th1 cytokine production ($\uparrow$ IL-12 receptor B2, $\uparrow$ IL18)
 - $\downarrow$ Th2 cytokine production
 - Thus
 - STAT-4 $\uparrow$ IL-12R and IL-18
 - STAT-6 and GATA-3 $\uparrow$ IL-4, IL-5 and IL-13 (Th2 cytokines dendritic cells (DCs])

Useful background: Q&As

Q1. The gastrointestinal tract has physiological as well as immunologic barriers. In the context of immune – mediated non-toxic reactions to food, outline the physiologic and immunologic barriers of the GI tract.

A1:

- Lumen
 - pH
 - pepsin, trypsin
 - bile acids
- Membrane
 - Columnar intestinal epithelial cells (IECs; non – professional antigen – presenting cells [APCs])
 - Tight junctions (TJs)
 - Mucus
 - Trefoil factors from stomach (TFF1, TFF2) and intestine (TFF3)
 - Defensins

- Lipid composition of brush border (apical) membrane (AM)
- Normal epithelial cell turnover
- AM peptidases

➤ Motility

➤ GALT/ MALT

- Innate immunity
 - NK (natural killer) cells
 - PMNs (polymorphonuclear leucocytes)
 - Macrophages
 - Epithelial cells
 - TLRs (protease – resistant proteins secreted by stomach [TLR1/2] and intestine [TLR3])
- Adaptive immunity
 - IEL intraepithelial lymphocytes
 - LP-L (lamina propria lymphocytes)
 - Peyer's patches
 - S-IgA (secretary IgA)
 - Cytokines
- Immune suppression (tolerance)
 - Main players: dendritic cells, IECs, Tregs (regulatory T cells)
- Main function of GALT
 - High dose tolerance: binding of antigen to receptor of T cells, with no costimulatory signals → energy of lymphocytes
- Low – dose tolerance – function of Tregs
 - Types of Tregs
 - CD4+ Th3 → TGF- β
 - CD4+ Th₁ → TL-10

- $\gamma\delta$ T cells $\rightarrow$ CD4+ 25+ Treg
- CD 8+ Ts (suppressor T cells)

Useful background:

- The eosinophils in the bone marrow mature under the influence of the hematopoiesis-specific transcription factors
 - GATA-1
 - GATA-2
 - PU1
 - C/EBP (enhancing binding protein family)
- The bone marrow is also stimulated to produce and release eosinophils to the peripheral blood by
 - Eotaxin
 - GM-CSF
 - GATA-192
 - C/ERP
- Eosinophils are directed to traffic to the gut site of allergen exposure
 - IL-5
 - Eotaxin
- Eosinophils release
 - EDEPs (eosinophil-derived granule proteins)
 - ECP (eosinophil cationic protein)
 - EDP (eosinophil derived neurotoxin)
 - EPO (eosinophil peroxidase)
 - MBP (major basic protein)
- These EDGP cationic proteins have
 - Antiviral activity
 - Ribonucleus activity
 - Degranulate mast cells

Useful background: Q&As

Q: Outline the pathogenesis of Eosinophilic Gastrointestinal Disorders

A:

- Ingestion of allergen
- $\alpha_4\beta_7$ – integrin and β_2 -integrin pathway control the movement of eosinophils into the small and large intestines.
- Eosinophils are bilobed nucleated granulocyte(s) which differentiate from myeloid progenitor cells into mature eosinophils which contain bright birefringent cationic granules which have a high affinity for the acidic dye eosin

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, page 425, Ninth Edition, 2010

Food Allergies

Useful Background: Definitions

- Adverse food reaction
 - “any untoward reaction occurring after the ingestion of a food or a food addition.....”
 - “.....and may be the result of toxic or non-toxic reactions”
- Toxic reactions
 - “will occur in any exposed individual upon ingestion of a sufficient dose.”
- Non – toxic reactions
 - “.....depend on individual susceptibilities....”
 - “.....may be immune – mediated....or non – immune – mediated”
- Immune – mediated non – toxic reactions – food allergy or hypersensitivity
- Non – immune – mediated non – toxic reactions – food intolerance

Source: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, page 139, Ninth Edition, 2010.

SO YOU WANT TO BE A GASTROENTEROLOGIST! – Food allergies

Q. Give 5 clinical or laboratory features associated with IgE-mediated food – induced symptoms.

- A.
- Atopy
 - Atopic dermatitis
 - Allergic rhinitis
 - Allergy
 - ↑ serum
 - IgE
 - Eosinophils
 - ↓ serum
 - Hemoglobin/ iron
 - Albumin
 - Positive skin prick tests

Useful background: Q&As

Q. The failure to develop normal oral tolerance, or the loss of oral tolerance, results in the development of food allergy. Outline the steps in IgE – and non-IgE-mediated food allergy.

- A. ➤ IgE-mediated food “allergy”
- APCs, T and B cells act with MHC class II molecules to present T cell epitopes (small peptide fragments) to the T cells as peptide – MHC complex.
 - T cells with the appropriate TCR (T cell receptor) bind the peptide – MHC complex
 - Binding of the peptide – MHC complex to TCR results in
 - Proliferation of T cells
 - Production of cytokines
 - IL-4 IgE response
 - IL-4 IgE activates Th2 cells.
 - Th2 cells act on B cells with the appropriate antigen-specific receptors.

- The B cells produce antigen-specific IgE antibodies.
 - Antigen-specific IgE antibodies binds to Fc I & II receptors on APCs (macrophages, mast cells, basophils).
 - Histamine, prostaglandins, leukotrienes are released.
 - The APCs are prepared for their next exposure to the antigen in question.
 - Normally there is tolerance:
 - ↑ secretion of IgA & IgG
 - ↓ systemic T-cell responses
 - In genetically predisposed persons, the release of these mediators leads to immediate hypersensitivity
 - Vasodilation
 - Smooth muscle contraction (bronchospasm)
 - Mucus secretion
 - The activated mast cells may also release cytokines leading to late-phase inflammation.
 - With subsequent exposure to the same dietary antigen, soluble proteins are presented to Th1, Th2 and Th3 (regulatory) cells.
- Non – IgE – mediated food “allergy”
- APC ± T cells become active and secrete.
 - TNF – α , and result in dietary protein – induced enterocolitis syndrome (cow's milk, soy protein)
 - IL-4 ± IL-5, and result in allergic eosinophilic gastroenteritis

Oncogenesis

Useful background: Q&As

Q. Give the cellular processes through and by which a balance of cell growth is achieved, describe the programs which trigger apoptosis and control proliferation, and use colorectal cancer as an example of the disruption of normal cell proliferation leading to oncogenesis.

➤ Cell growth

- Proliferation
- Differentiation
- Senescence
- Apoptosis (programmed cell death)

➤ Apoptosis

- Membrane – bound death receptors (THF-R, Fas and DR5)
 - Activate caspase 8
 - Caspase 8 activates BID (bd-2 interacting domain)
- Activation of expression of the tumour suppression gene TP53, ↑ bax/bcl-2 ratio
 - Caspases are intracellular cysteine proteases
- These proteases act out the aspartate residues of their substrates
 - The pro apoptotic bax and bak and the antiapoptotic bcl-2 and bcl-1 converge on the mitochondria
 - The mitochondria release cytochrome c
 - The apoptosome
 - Formed from cytochrome c, caspase 9 and Apaf 1
 - Activates several caspases, which lead to cell death (apoptosis)
- Histological features of apoptosis
 - Cytoplasm
 - Condensed, convoluted
 - Nucleus
 - Chromatin condensed
 - Convoluted
 - Fragmentation
 - Cell surface
 - Convoluted
 - Membrane – bound, cell residue – filled apoptotic bodies

➤ Proliferation

- Proliferation occurs when cells transition from G0 arrest into the active cell cycle.
- Proliferation is achieved by external stimuli acting through regulatory peptide growth factors, extracellular matrix molecules, and cell – cell adhesion molecules.
- The adhesion molecules (e.g., integrins, adherins, selectins, proteoglycans) modulate external growth stimuli, and thereby the cytoskeleton of the cell.
- There are 3 main types of receptors on the surface of cells which initiate cell signaling and alter the transcription of genes.
 - Tyrosine kinases
 - Serine and threonine kinases
 - G-protein coupled receptors
- Two examples of signaling pathways which regulate the cell cycle and proliferation of intestinal epithelial cells include
 - Wnt- β -catenin - $\downarrow$ p21 - $\uparrow$ proliferation extracellular EGF, CSF-1, PDGF, and
 - IGF- $\uparrow$ cyclin D1 gene expression
- Proliferation may be balanced by growth – inhibiting signals, e.g.
 - TGF- β mediated arrest of the cell cycle at the G1 phase by the induction of the transcription of p¹⁵, p²¹ and p27K1P1

CLINICAL PHYSIOLOGICAL CHALLENGE – CRC

Case: A 65 year old man presents with colorectal cancer (CRC). He wishes to know whether his family is at risk. Give the genes associated with CRC.

Answer:

- Three types of genes are induced in the transformation of normal to malignant cells:
 - Oncogenes ($\uparrow$ cell growth)
 - Tumour suppressor genes ($\downarrow$ growth)
 - DNA repair genes ($\uparrow$ genome instability)

Oncogenesis – associated genes and colorectal cancer

- Oncogenes
 - Genes which encode
 - A normal cellular protein to be produced in ↑ amounts, or
 - An abnormal, structurally altered protein with ↑ activity
 - Activation of oncogenes (proto-oncogenes → oncogenes):
 - Gene transduction/ insertion
 - Gene rearrangement
 - Gene amplification
 - Point mutation
 - RAS genes (related to G proteins), H-RAS, K-RAS and N-RAS, encode 21-kd proteins
 - Half of CRCs have point mutations in K-RAS
 - RAS activation leads to phosphorylation of serine and threonine kinases
 - C-Myc is a member of the myc family of nuclear oncogenes which may be overexpressed in GI cancers
 - Mutations in tumour suppressor genes alter the normal function of these genes, such as
 - The APC gene which inhibits Wnt signaling; the MEN 1 gene which regulates histone methyltransferase; E-cadherin, which interrupts cell - cell interactions
 - SMAD4, which is included in the transduction of TGF-β,
 - TP53 which regulates DNA repair and apoptosis
- Tumour suppressor genes may undergo gene deletions; these gene deletions lead to polymorphisms, which on a molecular level distinguish between paternal and maternal alleles.
- These polymorphisms include
 - SNPs (single nucleotide polymorphisms)
 - RFLPs (restriction fragment length polymorphisms)
 - Microsatellite polymorphisms

- On allelic deletion (aka loss of heterozygosity [LOH]) is the loss of an allele from one parent.
- This allelic deletion or LOH causes inactivation of some tumour suppressor genes.
- P53 is a nuclear phosphoprotein, end point mutations in the TP53 gene is seen in over half of sporadic CRC.
- The DNA mismatch repair system connects the spontaneous mismatching of nucleotides arising from slippage of microsatellite DNA.
- This slippage of microsatellite DNA occurs during the normal replication of DNA, leads to strand.
- The APC gene (adenomatous polyposis coli gene) is part of the chromosomal instability pathway leading to CRC.
- Germline mutations of APC are seen in FAP (familial adenomatous polyposis), and somatic APC mutations are seen in most sporadic CRCs.
- A premature stop code is produced, and the resulting protein product is truncated, and is associated with functional changes in important protein-protein interactions

Visceral pain

Transmission of ascending visceral pain

- First-order neurons
 - visceral C-fibers → thoracolumbar sympathetic nervous system → dorsal horn of spinal cord
- Second-order neurons
 - Cross the spinal cord
 - Ascend in
 - Spinothalamic pathway tracts
 - Spinoreticular pathway tracts
 - Reticulothalamic tracts

- Synapse of second – order neurons in the thalamus with third – order neurons which synapse in the limbic system.
 - Sensory – discriminative component:
 - Insula – input from sensory thalamus and nucleus tractus solitaries
 - Integrates sensory and emotional information
 - ACC (anterior cingulate cortex) – modulates affective component of pain
 - Primary somatosensory cortex
- Visceral afferent fibers
 - Parasympathetic
 - Vagus (→ medulla)
 - Pelvic nerves (→ S2 to S4)
 - Sympathetic
 - Superior cervical ganglion (T1 to T4)
 - Celiac ganglion (T5 to T12)
 - Superior mesenteric ganglion (to celiac ganglion)
 - Inferior mesenteric ganglion (L1 to L3)
- Descending modulation of pain
 - Endorphin -/ enkephalin – mediated inhibitory system
 - Cortex/ limbic system → midbrain/ medulla → dorsal horn of spinal cord
 - Directly inhibits nociceptive projection on second – order neurons
 - Indirectly inhibits spinal cord interneurons
 - Dorsal horn of cortex modulates (↑ or ↓ transmission ; gate control theory) the amount of input from the gut to the peripheral afferents.
 - The descending inhibition of afferent nociceptive impulses from peripheral sites is achieved through the serotonergic and epinephrine pathways, modifying endorphin activity.
 - These descending inhibitory systems are diffuse (DNIC [diffuse noxious inhibitory control], and are not activated normally in functional abdominal pain [FAP]).

- In FAP, there may be ↑ afferent signals, and ↓ descending pain control, producing hypersensitivity (↑ pain response) to a painful signal, possibly due to cleavage in the serotonin (5-hydroxytryptamine [5-HT]) receptors, 5-HT₁, 5-HT₃, 5-HT₄ or 5-HT reuptake.
- Also, the ACC (anterior cingulate cortex, the cortical motivational –affective component) is abnormal in FAP/ IBS (irritable bowel syndrome).

Functional abdominal pain syndrome (FAPS)

- The explanation of FAPS arises from the biopsychosocial model of illness, with the experiencing of pain arising from physiological, psychological (emotional) and cognitive (CNS – gut neuraxis) components
- There is
 - Upregulation of nociceptors in the mucosa
 - Sensitization of the visceral afferent nerves
 - Increased visceral efferent nerve signals in the brain (brain – gut dysregulation)
- Components may include
 - Dysregulation of CNS – ENS (central [C] and enteric [E] nervous systems)
 - ↑ pain perception
 - ↓ coping strategies
 - ↓ social networks

Avoid Common Mistakes!

- It is often suggested clinically that it is important to avoid the use of narcotics and benzo's in IBS and FAP

- The basis for this concept:
 - Narcotics and “benzo’s” (benzodiazepines) must be avoided in FAP/ IBS
 - ↑ pain sensitivity
 - ↓ pain threshold
 - ↑ dependency
 - Narcotic bowel syndrome
 - Do not withhold analgesia in person with an “acute abdomen”, since several (6) studies have shown that giving such patients sufficient pain-relieving analgesia does not delay the making of the correct diagnosis of the cause of the acute pain.
- Another common mistake
 - Surgical lysis of adhesions for chronic post-operative pain: “avoid laparoscopic adhesiolysis”. The problem is, this common clinical recommendation is not evidence – based

Useful background: Q&As

Q. In the context of the patient with intra-abdominal pathology, what is the Kehr sign, and what is its mechanism?

A:

- Any cause of irritation of the diaphragm, for example from a subdiaphragmatic abscess, hematoma, or splenic rupture, the pain may be referred to the left shoulder.
- “Referred pain is ordinarily located in the cutaneous dermatomes that share the same spinal cord level as the affected visceral inputs” (Yarze JC & Friedman LS. S/F page 163)

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